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Individuals with high bone mass have an increased prevalence of radiographic knee osteoarthritis

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ABSTRACT

We previously reported an association between high bone mass (HBM) and a bone-forming phenotype of radiographic hip osteoarthritis (OA). As knee and hip OA have distinct risk factors, in this study we aimed to determine (i) whether HBM is also associated with knee OA, and (ii) whether the HBM knee OA phenotype demonstrates a similar pattern of radiographic features to that observed at the hip.

HBM cases (defined by DXA BMD Z-scores) from the UK-based HBM study were compared with unaffected family controls and general population controls from the Chingford and Hertfordshire cohort studies. A single blinded observer graded AP weight-bearing knee radiographs for features of OA (Kellgren–Lawrence score, osteophytes, joint space narrowing (JSN), sclerosis) using an atlas. Analyses used logistic regression, adjusting *a priori* for age and gender, and additionally for BMI as a potential mediator of the HBM–OA association, using Stata v12.

609 HBM knees in 311 cases (mean age 60.8 years, 74% female) and 1937 control knees in 991 controls (63.4 years, 81% female) were analysed. The prevalence of radiographic knee OA, defined as Kellgren–Lawrence grade ≥ 2, was increased in cases (31.5% *vs.* 20.9%), with age and gender adjusted OR [95% CI] 2.38 [1.81, 3.14], $p < 0.001$. The association between HBM and osteophytosis was stronger than that for JSN, both before and after adjustment for BMI which attenuated the ORs for knee OA and osteophytes in cases *vs.* controls by approximately 50%.

Our findings support a positive association between HBM and knee OA. This association was strongest for osteophytes, suggesting HBM confers a general predisposition to a subtype of OA characterised by increased bone formation.

Introduction

The nature of the relationship between bone mineral density (BMD) and osteoarthritis (OA) remains a topic of debate [1]. While epidemiological studies have consistently demonstrated an association between higher BMD and both prevalent [2–5] and incident [6–8] radiographic OA of the large joints, the mechanisms behind these associations remain unclear; understanding these mechanisms will be key to translating research findings into therapeutic benefit [1]. To address this question from a novel perspective, we set out to investigate the prevalence and phenotype of OA in our cohort of high bone mass (HBM) individuals [9], compared with a control group. HBM individuals have extreme elevations in BMD likely to be genetically determined [9,10] and thus present from early adulthood, constituting a unique population for the investigation of causal pathways between BMD and OA. We have recently shown that HBM is associated with both an increased prevalence of self-reported joint replacement [11], and an increased prevalence of radiographic hip OA with a predominance of bone-forming features (osteophytosis

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and subchondral sclerosis) [12]. HBM is also associated with other characteristics which may potentially contribute to a higher risk of OA, including increased body mass index (BMI) [13].

While hip and knee OA both increase with age [14], evidence suggests that OA at these two joint sites has different determinants [15]. In particular, whereas local mechanical factors acting at the joint level may be more important for hip OA [16], knee OA has a stronger association with OA at other joint sites such as the hand [14,17] suggesting a more generalised systemic predisposition to the disease. The concept of knee and hip OA as different diseases is supported by the fact that hip OA appears to be more heritable than knee OA [18], and genetic studies indicate little genetic correlation between the two disorders [19]. The role of specific risk factors for OA at these two joint sites is also thought to differ; for example, the relationship between obesity and OA is reported to be stronger at the knee compared with the hip [15,20,21], and knee OA is more prevalent in females than males [14]. We therefore wished to establish whether any relationship between HBM and OA of the knee is similar to that previously observed at the hip.

The aim of this study was to investigate radiographic knee OA in our HBM population, determining i) whether HBM is associated with an increased prevalence of radiographic knee OA, ii) the phenotype of knee OA in HBM compared with controls in terms of individual radiographic features, and iii) the role of potential mediators such as BMI. We hypothesized that, in line with our previous findings and evidence from general population studies, HBM would be associated with a bone-forming phenotype of radiographic knee OA.

Methods

The HBM population

HBM cases were recruited as part of the UK-based HBM study, a multi-centre observational study of adults with unexplained HBM. Index cases were initially identified by screening DXA databases for T and/or Z-scores $\geq +4$. All DXA images were inspected by trained clinicians in order to exclude scans with artefactual elevation of DXA BMD, resulting in 49.4% of scans being excluded due to degenerative disease/osteoarthritis/scoliosis, and a further 15.5% for other reasons including surgical/malignant/Pagetic artefacts etc. Then, in order to identify generalised HBM, 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 $\geq +1.2$. A $+3.2$ threshold was consistent with the only published precedent for identifying HBM using DXA [22]. L1 Z-score was used to avoid misclassifying individuals with lower lumbar OA as having HBM [9,23]. Z rather than T-score limited age bias.

Further HBM cases were identified through DXA assessment of the relatives and spouses of index cases. In first-degree relatives, 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, with remaining unaffected first-degree relatives/spouses forming a family control group. Full details of this DXA database screening and recruitment have been previously reported [9]. Assessments, including a structured interview and clinical examination, were identical in both HBM cases and controls, and AP weight-bearing knee X-rays were performed in all participants 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 [24] 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 population controls, using age and gender-stratified random sampling.

Population-based controls

Population controls were selected from the Chingford 1000-women study (ChS) and Hertfordshire cohort study (HCS). The ChS is a prospective longitudinal female population-based cohort which initially recruited 1003 women aged 45–64 from the age/sex register of a general practice in Chingford, North-East London [2]; 20-year follow-up has recently taken place. AP knee radiographs were obtained in years 1, 5, 10, 15 and 20. 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). A single radiograph per participant was included in our study, with controls in the upper age bands selected first to ensure sufficient numbers of available films.

The HCS [25] 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) [26]; these individuals (207 men and 203 women now aged between 71.5 years and 80.6 years) had AP pelvis +/− weight-bearing knee 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. Files were automatically relabelled with anonymised codes, and presented in a random order to ensure blinding of the assessor. Radiographs were graded by a single observer (SH) following focussed radiological training. X-ray images were viewed and quantitative measurements made using open source ImageJ software [27]; semi-quantitative assessments were recorded within a Microsoft Access database.

Each knee was first assigned a global Kellgren–Lawrence OA grade [28], followed by semi-quantitative grading of individual radiographic features of OA using an established atlas [29] (Table 1); the presence or absence of chondrocalcinosis (previously shown to be associated with radiographic knee OA and osteophytosis [30]) was also noted (0–1). Each of these features was recorded separately in the medial and lateral compartments. For knees with OA (KL grade ≥ 2) only, the compartments affected (medial/lateral/both) were recorded. As all radiographs were performed AP, only the tibiofemoral joint was assessed.

A Kellgren–Lawrence grade of 2 (at least 1 definite osteophyte) defined the presence of OA in the main analysis; however, because

Table 1
Semi-quantitative scoring of radiographic features of knee osteoarthritis. Grading of individual radiographic features (except chondrocalcinosis) was performed using an atlas [29]. KL (Kellgren–Lawrence) grades defined as 0 — no features of OA, 1 — doubtful osteophyte, 2 — definite osteophyte, 3 — definite osteophyte plus narrowing, 4 — osteophyte/narrowing/deformity as in Spector 1993 [34]. OA = osteoarthritis, OP = osteophyte, JSN = joint space narrowing.

OA feature	Categorical grading	Binary variable (s)
KL grade (global knee OA)	0–4	KL grade ≥ 2 (OA present), KL grade ≥ 3 (moderate OA)
Medial compartment osteophyte	0–3	Any osteophyte
Lateral compartment osteophyte	0–3	(any OP grade ≥ 1), moderate osteophyte (any OP grade ≥ 2)
Medial JSN	0–3	Any JSN (JSN grade ≥ 1),
Lateral JSN	0–3	moderate JSN (JSN grade ≥ 2)
Medial sclerosis	0–1	Subchondral sclerosis
Lateral sclerosis	0–1	(grade ≥ 1)
Medial chondrocalcinosis	0–1	Chondrocalcinosis
Lateral chondrocalcinosis	0–1	(grade ≥ 1)