**Introduction**

Osteoarthritis (OA) is the most common joint disorder in the elderly and is characterized by cartilage degradation, new bone formation, and changes in subchondral bone [1] with bone playing a key role in pathogenesis. Population-based studies have established that patients with radiological findings of hip and knee OA have an elevated bone mass of 3–6% (depending on site of OA and areal bone mineral density (BMD) measurement) compared with control subjects [2]. Furthermore, some studies show patients with OA to have a decreased risk of fracture [3] although others demonstrate no association or even an increased fracture risk [5].

Associations between aBMD and radiographic OA appear strongest for the bony features of OA, such as osteophytes, rather than with joint space narrowing (JSN) [5, 6]. Similarly, features of OA reflecting excess bone formation (osteophytes and sclerosis) were also more strongly associated with high bone mass [7]. Taken together, these results suggest that the relationship between OA and bone health may be driven mainly through associations with osteophytes and sclerosis.

As higher aBMD in individuals with osteoarthritis is not only found within the affected joint, we hypothesised that volumetric BMD (vBMD) at sites distant to the hip would be higher and bone microarchitecture may be modified in participants with radiographic osteophytes and sclerosis, reflecting a tendency towards a systemic bone-forming phenotype. Furthermore, in this exploratory study, we aimed to investigate whether these differences would be found solely within weight bearing bones, such as the tibia, or additionally in non-weight bearing bones, such as the radius.

**Method**

**Study population**

The Hertfordshire Cohort Study (HCS) is a population-based UK cohort of older adults. Study design and recruitment have been described in detail previously [8]. In brief, we traced men and women born between 1931 and 1939 in Hertfordshire and who still lived there in 1998–2003 when a nurse-administered questionnaire and clinic visit were carried out. Participants were not selected on the basis of musculoskeletal pathology, but represented individuals born in a geographic region who continued to live there. In 2011-2012, 592 men and women from the geographical area of East Hertfordshire were invited to take part in an OA study that was designed to consider the personal burden of OA. A home visit which included a structured interview was conducted in 443 patients and bilateral hip radiographs were performed. Of these, 350 agreed to have a HRpQCT scan one year later (in 2012-3). A total of 318 participants had both hip radiographs and HRpQCT undertaken. The East and North Hertfordshire Ethical Committees granted approval for the study.

**Radiographic assessment and definition of hip OA**

Bilateral radiographs of the hips (standing anteroposterior) were obtained and graded by experienced reviewers following focussed training. Semi-quantitative scores for the Croft grade were converted to binary variables for analysis; a Croft grade of ≥3 defined the presence of radiographic OA. The presence of JSN, sclerosis and osteophytes were assessed in accordance with the OARSI atlas as binary variables [9]. Hip x-rays were assessed by 4 experienced reviewers. For hip OA, inter-observer agreement was 72% with a kappa statistic of 0.46 consistent with moderate agreement. For individual components of OA, inter-observer agreement ranged from 67-100% with between fair and perfect agreement.

**High-resolution peripheral quantitative computed tomography**

Distal radial and tibial HRpQCT (XtremeCT, Scanco Medical AG, Switzerland) scans were carried out of the non-dominant side except when it had previously fractured. Antero-posterior 2D scout views were performed to determine the region to be imaged. All scans were acquired in keeping with the manufacturer’s guidelines and as described by Boutroy *et al.* [10], assessed for motion artefact and repeated if necessary. Eight tibial scans and 39 radial scans were excluded due to excessive motion artefact.

Image analysis was carried out using the standard manufacturer’s method which has been described in detail previously [11]. Standard morphologic analysis produced trabecular BMD (Tb.vBMD, mg/cm³), trabecular number (Tb.N, per cm), trabecular thickness (Tb.Th, µm) and trabecular separation (Tb.Sp, µm). Each measure has been validated against micro-CT imaging. Further analysis was performed using an automated segmentation algorithm. Assessments were made of cortical area (Ct. Area, mm²), cortical density (Ct.vBMD, mg/cm³), and cortical porosity (Ct.Po, %). Cortical thickness (Ct.Th, µm) was determined from the threshold cortex image using a distance transform after removal of intracortical pores. Short term precision values (% CV) for cortical and trabecular BMD have been shown to range from 0.3 to 1.2 [12]. The effective dose to the subject during each scan was <3μSv.

**Assessment of demographic and lifestyle variables**

Height was measured to the nearest 0.1 cm using a wall-mounted SECA stadiometer and weight using electronic scales to the nearest 0.1kg, on the day of scanning. Body Mass Index (BMI) was calculated as weight/height² (kg/m²). Smoking status and alcohol consumption were available from the nurse-administered questionnaire as part of the OA study.

**Statistical methods**

Statistical analyses were performed using STATA 13.1. Descriptive statistics for continuous variables are expressed as mean (standard deviation) and categorical variables as frequency (percentage). Differences in continuous variables between men and women were assessed using Student’s t-tests and in categorical variables using Pearson’s Χ² test or Fisher’s exact test, as appropriate. Linear regression was used to examine the associations between the presence of JSN and HRpQCT bone parameters. Participants were then grouped into those with no bony changes, osteophytes alone, and both osteophytes and sclerosis. Linear regression was used to assess for differences in HRpQCT bone parameters between each of these three groups separately. All regression analyses were undertaken with and without adjustment for the a priori covariates of age and BMI.

**Results**

**Characteristics of study participants**

The mean(SD) age of participants was 76.1(2.5) and 76.4(2.6) years in men and women, respectively (Table 1). Rates of smoking were higher in men than women (p<0.001); 58.2% of men (n=99) and 37.8% of women (n=56) were current or ex-smokers. Alcohol consumption was also greater in men (p<0.001). Prevalence of radiographic hip OA (Croft score ≥3), sclerosis and JSN did not differ significantly by sex whereas osteophytes were more common in men than women (n=119 (70.0%) vs. n=84 (56.8%); p=0.014).

**Bone geometry, volumetric bone mineral density and microarchitecture**

Tb.vBMD and Tb.Th both tended to be higher in men with bony changes. However, these differences only reached statistical significance for osteophytes alone with Tb.vBMD in the distal radius and Tb.Th in both the distal radius and tibia (p<0.05 in each case) (Table 2 and 3; Figure 1). These relationships were maintained after adjustment for age and BMI.

In the tibia, men with both sclerosis and osteophytes had higher Ct.vBMD (mean(95%CI) 897.5(877.5,917.5)mg/cm3) than in those with no bony changes (865.2(847.7,882.7)mg/cm3) and osteophytes alone (860.8(846.3,875.3)mg/cm3) (p<0.05). This relationship was maintained after adjustment for age and BMI. A similar trend was shown for tibial Ct.Th although only the difference between osteophytes alone (mean(95%CI) 1180(1122,1239)µm) and osteophytes and sclerosis (1301(1203,1400)µm) reached statistical significance prior to adjustment (Table 3).

Conversely, in the tibia those with osteophytes and sclerosis had lower cortical porosity than those without bony changes (p<0.05) (Figure 1). This association was fully attenuated by adjustment for covariates. No associations were found, at either the radius or tibia, between bony changes in the hip and HRpQCT parameters in women, nor between JSN and HRpQCT parameters in either sex, before or after adjustment for covariates (results not shown).

**Discussion**

In this study, we utilized HRpQCT to investigate bone parameters at the distal radius and tibia in a cohort of older men and women with and without radiographic features of hip OA including JSN, osteophytes, and sclerosis. We found higher Tb.vBMD and Tb.Th in men with osteophytes, whereas the presence of sclerosis, in addition to osteophytes, was associated with higher tibial Ct.vBMD and Ct.Th than in those with osteophytes alone.

This is the first study to investigate relationships between bone parameters assessed by HRpQCT and radiographic features of hip OA. Our findings suggest that bone-related components of hip OA may be associated with systemic bone density and microarchitecture. In accordance with our results, Hardcastle et al. [7] recently demonstrated that features of OA reflecting excess bone formation were more strongly associated with high bone mass case status than other OA features (such as JSN) suggesting that increased bone formation is a key feature of the “bone forming” phenotype as previously postulated [13].

These findings are also in keeping with the study by Chaganti et al which showed positive associations between an osteophyte-predominant form of radiographic hip OA and both cortical and trabecular vBMD within the total hip using quantitative computed tomography (QCT) [14]. However, the current study suggests potential associations at peripheral sites instead and additionally separates out individuals with osteophytes alone from those with both osteophytes and subchondral sclerosis. Consequently it has been possible to show the novel findings that, in men, the presence of osteophytes was associated with trabecular parameters whereas the presence of sclerosis was associated with cortical parameters. This suggests different underlying mechanisms linking these two bony components of OA with systemic bone health. It is well established that trabecular bone is modelled by the endochondral ossification system which has also been implicated in osteophyte formation, whereas the link between cortical bone health and subchondral sclerosis may lie with a common propensity to respond to mechanical stimuli.

The nature of these different mechanisms is however yet to be elicited and it also remains to determine why associations were identified in men but not women. It may be related to differences in patterns of physical activity with a greater role played in men than women. Hormonal factors could also be implicated in this sexual dimorphism.

We might hypothesise that those with lower Ct.vBMD and Ct.Th may therefore be relatively protected from progressing from osteophytes alone to the addition of sclerosis. Interestingly, this association was found in the tibia but not the radius. This might be due to commonality of weight bearing in the tibia and the hip or to the greater precision with which tibial parameters can be measured reducing the risk of type II error.

Plausible mechanisms to explain the link between OA and bone structure in general include common genetic risk factors, including variants in growth factor and Wnt signalling pathway genes, known to regulate bone mass and linked to OA in candidate gene studies [15]. Increased periarticular bone could itself lead to the development of OA either through mechanical effects on the overlying cartilage or molecular cross-talk between bone and cartilage [16].

This study does have both strengths and limitations. Firstly, the cohort in which this study was completed comprises men and women born as singleton births between 1931 and 1939. It is well phenotyped allowing adjustment for potential covariates and it has been shown to be fairly representative of the UK population by means of a comparison with the Health Survey for England. However, those studied were entirely Caucasian and recruited from one specific region of Hertfordshire. Thus, extrapolation of the findings to other ethnic groups and regions is uncertain. Secondly, there was little time between measurement of bone health and assessment of hip disease which makes attribution of causality difficult. Thirdly, bone microarchitecture was studied in the extremities rather than within the hip itself which clearly limits evaluation of direct local associations. Lastly, due to the study design, including the use of multiple testing, this study is purely exploratory and hypothesis generating. This must be taken into account when interpreting the findings, which certainly require replication in larger cohorts.

In summary, this study shows higher Tb.vBMD and Tb.Th in men with osteophytes, and higher tibial Ct.vBMD and Ct.Th in men with sclerosis, as well as osteophytes, in the hip joint. However, further research is required to confirm whether these findings represent true biological associations. It would be of particular interest to explore the associations in subjects with OA in different joints and to compare to bone microarchitecture at other sites. Identification of the potential mechanisms, acting through cortical and trabecular remodelling, is likely to improve our understanding of the pathogenesis of bony changes in patients with OA and may eventually lead to a targeted treatment.

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**Author contributions**

MHE, JP, KAW, KAJ, CC and EMD made substantial contributions to the conception and design of the study, interpretation of data, drafting the article or revising it critically for important intellectual content and final approval of the version to be submitted. MKJ and CM made substantial contributions to the interpretation of data, revising the article critically for important intellectual content and final approval of the version to be submitted. JW made substantial contributions to the acquisition of data, revising the article critically for important intellectual content and final approval of the version to be submitted.

MHE (me@mrc.soton.ac.uk) and JP (julien.paccou@chru-lille.fr) take responsibility for the integrity of the work as a whole, from inception to finished article

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**Competing interest statement**

MHE, JP, KAW, KAJ, CM, JW, MKJ and EMD have no conflicts of interest to declare. Professor Cyrus Cooper has received consultancy fees and honoraria from Alliance for Better Bone Health, Amgen, Eli Lilly, GSK, Medtronic, Merck, Novartis, Pfizer, Roche, Servier, Takeda and UCB.

**References**

[1] Litwic A, Edwards MH, Dennison EM, Cooper C. Epidemiology and burden of osteoarthritis. Br Med Bull 2013;105:185-99.

[2] Nevitt MC, Lane NE, Scott JC Hockberg MC, Pressman AR, Genant HK et al. Radiographic osteoarthritis of the hip and bone mineral density. Arthritis Rheum 1995;38:907-16.

[3] Dequeker J, Johnell O. Osteoarthritis protects against femoral neck fracture: the MEDOS study experience. Bone 1993;14(Suppl1):S51-6.

[4] Vestergaard P, Rejnmark L, Mosekilde L. Osteoarthritis and risk of fractures. Calcif Tissue Int 2009;84:249–56.

[5] Castaño-Betancourt MC, Rivadeneira F, Bierma-Zeinstra S, Kerkof HJ, Hofman A, Uitterlinden AG et al. Bone Parameters Across Different Types of Hip Osteoarthritis and Their Relationship to Osteoporotic Fracture Risk. Arthritis Rheum 2013;65(3):693-700.

[6] Hannan MT, Anderson JJ, Zhang Y, Levy D, Felson DT. Bone mineral density and knee osteoarthritis in elderly men and women.The Framingham Study.Arthritis Rheum. 1993;36:1671-80.

[7] Hardcastle SA, Dieppe P, Gregson CL, Hunter D, Thomas GE, Arden NK, et al. Prevalence of radiographic hip osteoarthritis is increased in high bone mass. Osteoarthritis Cartilage 2014;22:1120-8.

[8] Syddall HE, Aihie SA, Dennison EM, Martin HJ, Barker DJ, Cooper C. Cohort profile: the Hertfordshire cohort study. Int J Epidemiol 2005;34:1234-42.

[9] Altman RD, Gold GE. Atlas of individual radiographic features in osteoarthritis, revised. Osteoarthritis Cartilage. 2007;15(Suppl A):A1-56.

[10] Boutroy S, Bouxsein ML, Munoz F, Delmas PD. In vivo assessment of trabecular bone microarchitecture by high-resolution peripheral quantitative computed tomography. J Clin Endocrinol Metab 2005;90:6508-15.

[11] Laib A, Hauselmann HJ, Ruegsegger P. In vivo high resolution 3D-QCT of the human forearm. Technol Health Care 1998;6(5-6):329-37.

[12] Paggiosi MA, Eastell R, Walsh JS. Precision of High-Resolution Peripheral Quantitative Computed Tomography Measurement Variables: Influence of Gender, Examination Site, and Age. Calcif Tissue Int. 2014;94:191-201.

[13] Lane NE, Nevitt MC. Osteoarthritis, bone mass, and fractures: how are they related? Arthritis Rheum. 2002;46:1-4.

[14] Chaganti RK, Parimi N, Lang T, Orwoll E, Stefanick ML, Nevett M et al. Bone mineral density and prevalent osteoarthritis of the hip in older men for the Osteoporosis Fractures in Men (MrOS) Study Group. Osteoporos Int 2010;21(8):1307-16.

[15] Smith AJ, Gidley J, Sandy JR, Perry MJ, Elson CJ, Kirwan JR, et. al. Haplotypes of the low-density lipoprotein receptor-related protein 5 (LRP5) gene: are they a risk factor in osteoarthritis? Osteoarthritis Cartilage. 2005;13:608-13.

[16] Lories RJ, Luyten FP. The bone-cartilage unit in osteoarthritis. Nat Rev Rheumatol. 2011;7:43-9.

**Table 1 Characteristics of study participants**

|  |  |  |  |
| --- | --- | --- | --- |
| Variables | Men(n=170) | Women(n=148) |  |
|  | Mean (SD) | Mean (SD) | p value |
| Age (years) | 76.1 (2.5)  | 76.4 (2.6) | 0.310 |
| Height (cm) | 173.8 (6.1) | 159.9 (5.9) | <0.001 |
| Weight (kg) | 82.2 (11.9) | 71.5 (12.6) | <0.001 |
| Body mass index (kg/m²) | 27.3 (3.6) | 28.0 (4.6) | 0.109 |
| Alcohol consumption(Units/week)1 | 7.0[1.75-14.0] | 0.5 [0.00-4.73] | <0.001 |
|  | n (%) | n (%) | p value |
| Smoking statusNeverFormerCurrent | 71 (41.8)92 (54.1)7 (4.1) | 92 (62.2)52 (35.1)4 (2.7) | 0.001 |
| Radiographic hip OA2  | 76 (44.7) | 54 (36.7) | 0.150 |
| Osteophytes | 119 (70.0) | 84 (56.8) | 0.014 |
| Sclerosis | 34 (20.0) | 18 (12.2) | 0.063 |
| JSN | 90 (52.9) | 87 (59.2) | 0.264 |

Key: 1Median [IQR]; 2Croft score ≥3.

**Table 2 - Radial bone microarchitectural parameters in men by bony features of hip osteoarthritis**

|  |  |
| --- | --- |
| **Bone parameter** | **Mean (SD)** |
| **No bony changes**(n=40) | **Osteophytes only**(n=76) | **Osteophytes & Sclerosis**(n=28) |
| Trabecular area (mm2) | 355.4 (60.5) | 350.5 (79.0) | 362.1 (60.8) |
| Trabecular density (mg/cm3) | 169.4 (26.7) | 184.5 (35.5) | 181.5 (34.0) |
| Trabecular thickness (μm) | 61.4 (8.3) | 65.6 (10.0) | 63.5 (9.4) |
| Trabecular number (cm-1) | 23.0 (2.0) | 23.4 (2.7) | 23.8 (2.3) |
| Cortical area (mm2) | 69.7 (12.6) | 70.3 (14.1) | 72.7 (11.7) |
| Cortical thickness (μm) | 808.6 (165.2) | 812.5 (186.4) | 831.5 (144.1) |
| Cortical density (mg/cm3) | 906.7 (51.4) | 905.6 (53.6) | 911.8 (41.9) |
| Cortical porosity (%) | 3.9 (1.2) | 4.1 (1.5) | 4.2 (1.3) |

**Table 3 - Tibial bone microarchitectural parameters in men by bony features of hip osteoarthritis**

|  |  |
| --- | --- |
| **Bone parameter** | **Mean (SD)** |
| **No bony changes**(n=46) | **Osteophytes only**(n=86) | **Osteophytes & Sclerosis**(n=29) |
| Trabecular area (mm2) | 764.0 (136.6) | 781.7 (162.3) | 738.9 (106.6) |
| Trabecular density (mg/cm3) | 182.0 (30.1) | 190.1 (37.3) | 191.7 (33.2) |
| Trabecular thickness (μm) | 61.2 (9.7) | 66.2 (10.4) | 65.7 (7.6) |
| Trabecular number (cm-1) | 24.9 (2.6) | 24.0 (3.3) | 24.3 (3.2) |
| Cortical area (mm2) | 143.2 (23.0) | 138.3 (30.8) | 149.0 (31.2) |
| Cortical thickness (μm) | 1207.8 (250.3) | 1180.2 (276.1) | 1301.1 (270.8) |
| Cortical density (mg/cm3) | 865.2 (60.4) | 860.8 (68.8) | 897.5 (55.1) |
| Cortical porosity (%) | 9.5 (2.8) | 9.3 (2.8) | 8.2 (2.7) |

Figure 1 - Radial and tibial microarchitectural parameters in men by bony features of hip osteoarthritis in men