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THE PREVALENCE OF RADIOGRAPHIC HIP OSTEOARTHRITIS IS INCREASED IN HIGH BONE MASS; A CASE-CONTROL STUDY

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Purpose: Numerous epidemiological studies have reported an association between increased bone mineral density (BMD) and osteoarthritis (OA), but whether this represents cause or effect remains unclear. To establish whether higher BMD predisposes to OA, we aimed to determine whether individuals with High Bone Mass (HBM) have a higher prevalence of radiographic hip OA compared with controls.
Methods: HBM cases were recruited from 15 UK centres by systematically screening DXA databases. HBM was defined in index cases as a total hip Z-score ≥+3.2 and L1 Z-score ≥+1.2, or vice-versa, and in first-degree relatives of index cases as total hip Z-score plus L1 Z-score ≥+3.2; unaffected relatives were recruited as controls. AP pelvic X-rays were performed in participants aged ≥40 years. Age-stratified random sampling was used to select further population controls from the Chingford 1000-women and Hertfordshire cohort studies. All radiographs were assessed for features of OA (Croft score, osteophytes, joint space narrowing (JSN), cysts, sclerosis) by a single observer blinded to case-control status using an atlas. Minimum joint space width (JSW) was measured using a computer-aided method. Intra-observer repeatability for most features was good. Analyses used logistic regression, with generalised estimating equations to account for within-person clustering (right/left), adjusted a priori for age, gender and body mass index (BMI).
Results: Analyses included 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), after excluding poor quality films and hip replacements (n=109). The prevalence of radiographic hip OA, defined as Croft score ≥3, was increased in cases compared with controls (20.0% vs. 13.6%). Results of logistic regression analyses for the binary radiographic OA variables in HBM cases vs. controls are shown in the table below, adjusted for age, gender and BMI. Cases had an increased odds of hip OA compared with controls after adjustment (OR 1.52 [1.09, 2.11], p=0.013). In analyses of individual radiographic features, osteophytes (both any osteophyte, and moderate (≥grade 2) osteophytes) and subchondral sclerosis were also more prevalent in cases compared with controls. However, the prevalence of JSN was not increased in HBM cases, and measured JSW did not differ between the groups (mean difference 0.04mm [-0.05, 0.13], p=0.39). Analyses were repeated in the different control groups separately, and stratified by gender, with broadly similar findings.

Logistic regression analysis of radiographic hip OA variables in HBM cases vs. all pooled controls.

Outcome	OR (95% CI) in HBM cases vs. controls	p value
Hip OA (Croft score ≥3)	1.52 (1.09, 2.11)	0.013
Any osteophyte (≥grade 1)	2.12 (1.61, 2.79)	<0.001
Any moderate osteophyte (≥grade 2)	2.39 (1.72, 3.33)	<0.001
Femoral osteophyte (≥grade 1)	1.60 (1.18, 2.17)	0.003
JSN (any)	0.97 (0.72, 1.33)	0.869
JSN (≥grade 2)	1.48 (0.82, 2.69)	0.196
Cysts	0.34 (0.08, 1.42)	0.139
Subchondral sclerosis	2.78 (1.49, 5.18)	0.001

Conclusions: An increased prevalence of radiographic hip OA was observed in HBM cases compared with both family and general population controls. In addition, those features of OA arising from increased bone formation, including osteophytes and subchondral sclerosis, were particularly strongly associated with HBM suggesting that hip OA in this group has a hypertrophic phenotype.

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COORDINATE AND SYNERGISTIC EFFECTS OF EXTENSIVE TREADMILL EXERCISE AND OVARIECTOMY ON ARTICULAR CARTILAGE DEGENERATION

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Purpose: Osteoarthritis (OA) is considered to be a multifactorial disease with factors such as chronic inflammation, aging, menopause, obesity, genetic background, and mechanical stress . For example, estrogen depletion by ovariectomy (OVX) is reported to accelerate cartilage degradation in young female mice. Too much mechanical stress on articular cartilage, which may be caused by overweight, joint instability, or over-exercise, is also reported to induce several catabolic factors for cartilage articular cartilage. These individual data clearly show that all these factors are involved in the pathogenesis of OA, however, orchestrated effects of these factors in OA progression are still unclear. To analyze the crosstalk between estrogen signal, which is systemic hormonal signal, and mechanical stress on articular cartilage homeostasis, we analyzed the severity of articular cartilage damage after treadmill exercise in OVX mice. Last year, we reported that degree of articular cartilage degeneration induced by extensive treadmill exercise was greatly exacerbated by OVX. In this study, to further analyze the molecular mechanism of articular cartilage degeneration induced by OVX and treadmill exercise, we performed detailed histomorphometrical analyses of articular cartilage.
Methods: Twenty-four female 8 week-old Balb/c mice were randomly divided into two groups, one was an OVX group (OVX), and the other was a control group (SHAM). Two weeks after the surgery, all the mice were subjected to forced running for 5 days at 12m/min for 10 minutes followed by 20m/min for 10 minutes to adopt treadmill exercise. Then each group was further randomly divided into two groups, 6 mice were subjected to forced running by treadmill (OVX+run or SHAM+run) and the latter 6 were left in cage ad libitum (OVX+cage or SHAM+cage). Running group was subjected to forced running for 6 weeks (5 days a week) at 12m/min for 10 minutes followed by 20m/min for 100 minutes. After 6 weeks, both left and right knee joints were harvested. Left knee was prepared for histology and immunohistochemistry. Integrity of articular cartilage and synovial membrane was assessed by Hematoxylin and Eosin (H&E) staining and immunostaining for type I and type II collagen. To evaluate the cell infiltration and synovial hyperplasia, H&E staining and F4/80 immunostaining were assessed. To assess cellularity of articular cartilage, we measured the area of chondrocyte, chondrocyte numbers and the size of chondrocyte using Zeiss Axio Vision Image Analysis system. To analyze the structural alteration and bone parameter after treadmill exercise and OVX, right knee joints were subjected for micro-CT analyses.
Results: Micro-CT analyses showed significant loss of metaphyseal trabecular bone volume/tissue volume (BV/TV) after OVX. Forced running always reversed the trabecular BV/TV and trabecular bone thickness of both metaphysis and epiphysis regardless of OVX. In the epiphyseal region, we did not observe osteophyte formation between the 4 groups. H&E staining of articular cartilage revealed that OVX and forced running respectively had subtle effect on cellularity and cell morphology of articular cartilage. However, the combination of OVX and forced running synergistically and significantly enhanced cellularity of articular cartilage. In addition, we observed the average size of articular chondrocytes was significantly increased in the OVX+run group (Fig. 1.2). H&E and F4/80 staining revealed that significant number of macrophages were infiltrated in the synovial membrane of OVX+run group. In contrast, we did not observe any sign of osteomyelitis in all the 4 experimental groups (Fig. 3).
Conclusion: In this study, we observed both cellularity and the size of articular chondrocytes were increased in the OVX+run group. These data suggest that mechanical stress and the loss of ovary function cooperatively enhanced proliferation and hypertrophic differentiation of articular chondrocytes. In addition, we observed extensive macrophage infiltration and hyperplasia in the synovial membrane but not in bone marrow in the OVX+run group while subtle inflammatory responses were observed in OVX+cage and SHAM+run groups. These