

A COTWIN CONTROL STUDY OF THE RELATIONSHIP BETWEEN HIP OSTEOARTHRITIS AND BONE MINERAL DENSITY

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Objective. Previous case-control studies have shown various degrees of inverse relationship between osteoarthritis (OA) and osteoporosis (OP). The aim of this study was to examine the relationship between radiographic hip OA and bone mineral density (BMD) at the affected and contralateral hips, as well as at more distal sites. We also explored the possibility that this association might be confounded by genetic factors.

Methods. Using the discordant twin model to reduce selection bias and adjust for genetic factors, plain pelvic radiographs of white female twins aged >40 years, from the St. Thomas' UK Adult Twin Register, were assessed for radiographic features of hip OA. Overall OA was classified using a 6-point global grading system (Croft). Osteophytes (OPH) and joint space narrowing (JSN) were also examined separately. BMD was measured by dual x-ray absorptiometry at the left hip, lumbar spine, and total body. The association of OA with BMD was assessed using conditional logistic regression. Adjustments were made for body mass index, lifetime physical activity, menopausal status, use of estrogen, and smoking.

Results. The analysis included a total of 1,148 women comprising 160 monozygotic and 414 dizygotic twin pairs. The median age of the twins was 53 years (range 40–70). The crude and adjusted odds ratios and 95% confidence intervals for having radiographic features of hip OA were 1.63 (1.06, 2.50) and 1.80 (1.05, 3.12), respectively, per unit difference in standardized BMD of the ipsilateral femoral neck. The presence of OPH, but not JSN, was associated with higher BMD.

Twins with hip OPH had 3.5% higher femoral neck BMD than their unaffected cotwins. No clear association was found between hip OA and BMD at the contralateral site, lumbar spine, or total body.

Conclusion. This twin study confirms the existence of an inverse relationship between OA and OP at the hip. However, the relationship was localized to the OA-affected hip. The generalized and greater increase in BMD in osteoarthritic subjects seen in previous studies of unrelated populations is therefore likely to be due, in part, to genetic factors shared by hip OA and high bone mass. It also suggests that local changes in bone density may be a component of the disease process in hip OA.

Interest in the relationship between osteoarthritis (OA) and osteoporosis (OP) first arose when surgeons in the 1960s noticed the general absence of osteoarthritic changes in femoral necks excised in the treatment of osteoporotic fractures of the femoral head (1,2). While the evidence is generally in favor of an inverse relationship between these 2 common disorders, there are still inconsistencies. In a recent review of the subject, Dequeker et al attribute the controversy to the different anatomic sites measured and the different methods used in evaluating and expressing the results, as well as to differences in subject selection leading to bias due to confounding (3). In large population studies, an increase in axial bone mineral density (BMD) of ~5–10% has been found consistently in relation to hip and knee OA (4–8).

The explanation of this inverse relationship remains unclear. Patients with primary OP and those with OA may differ anthropometrically (9). Moreover, potential risk factors for OA, such as weight, have a protective role in the development of OP (9), suggesting that OA and OP patients might arise from different genetic populations. It has been shown recently that OA trabecular bone is metabolically very active compared with normal tissue (10). The increased bone metabolism and deposition of collagen support the evidence of subchon-

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dral bone remodeling with resultant stiffening of the bone in OA, as has been suggested by Radin and colleagues (11,12). Since both OA and OP are strongly influenced by genetic factors (13,14), their relationship to each other may also be genetically determined to some extent. In previous studies, adjustments have been made for various confounding variables, but not for familial or genetic factors.

In the present study, we performed a matched case-control study using twin pairs discordant for OA to assess the relationship between hip OA and BMD at the affected hip and at more distal sites. We also evaluated bone density differences within pairs discordant for hip OA. The main advantage of using twins is the close matching for genetic and environmental factors within pairs that markedly reduces the effect of confounding variables, including potential confounding due to genetic factors.

SUBJECTS AND METHODS

Study population. The analysis used data from the St. Thomas' UK Adult Twin Register, consisting of unselected volunteers recruited through a national media campaign (15). Only white female twin pairs of age >40 years were included in the analysis. None of the women were known to have any disease causing secondary OA or OP, and all were broadly representative of the normal British population as discussed elsewhere (16). Ethical approval was obtained from the hospital ethical committee, and full informed written consent was obtained from all subjects. The data included anthropometric and lifestyle variables collected through a nurse-administered questionnaire. Zygosity was determined by a standard questionnaire and was confirmed when necessary by multiplex DNA fingerprinting.

Procedures. Pelvic radiographs were obtained with the subject in the supine anteroposterior (AP) position, with a standard tube-to-film distance of 100 cm and the feet positioned in 15° of internal rotation. A single observer blinded to the zygosity and pairings assessed the radiographs. If an abnormality was seen, the radiographs were read independently by a second observer, and if there was a discrepancy, the opinion of a third specialist was asked. The intraobserver reproducibility, tested on a subgroup of 350 of the twins, was estimated using a weighted kappa statistic and found to be very satisfactory, ranging from 0.81 to 0.84 for different radiographic features.

We used the Croft grading scale (17), which assesses the individual radiographic features of minimal joint space, presence of osteophytes (OPH), maximum thickness of subchondral sclerosis, and cyst formation. Minimal joint space and sclerosis were measured in mm along a radius from the center of the femoral head, the former as the shortest observed distance from the femoral head to the acetabulum and the latter as the maximum thickness. The presence of OPH was graded on a 4-point scale (0-3), using an atlas of individual features (18). Based on the individual features, the summary grade, according to Croft's grading scale, is as follows: grade 0 = no changes of OA; grade 1 = osteophytosis only; grade

2 = joint space narrowing (JSN) only (<2.5 mm); grade 3 = any 2 of osteophytosis, JSN, subchondral sclerosis (≥ 5 mm), and cyst formation; grade 4 = any 3 of osteophytosis, JSN, subchondral sclerosis, and cyst formation; and grade 5 = the same as grade 4, but with the addition of deformity of the femoral head. Twins with total hip replacement due to OA were classified as grade 5, with 0 mm minimal joint space. In the analysis, cases were defined by a minimum global grade of 1.

The individual features of OA, such as the presence of OPH and JSN, were also examined separately. Osteophytosis was defined as the presence of OPH of any grade, while JSN was defined as joint space of <2.5 mm.

BMD was measured at the nondominant hip (femoral neck, total hip), lumbar spine (L1-L4) in the AP projection, and for the total body using dual x-ray absorptiometry (QDR-2000 DXA scanner; Hologic, Waltham, MA). Reproducibility was assessed by performing duplicate scans of 40 normal volunteers and was 0.6-1.6% depending on the site scanned.

Confounding variables. Height and weight, measured with the subject in the standing position without shoes, were used to calculate the body mass index (BMI) in kg/m^2 . We also adjusted for lifestyle variables, using questionnaires to collect this information. Physical activity was determined by a combined measure of moderate physical activity currently and in the third decade of life. We used a 3-point scale (0-2) as follows: grade 0 = no physical activity; grade 1 = moderate physical activity either currently or in the third decade; and grade 2 = moderate physical activity both currently and in the third decade. Other variables adjusted for included smoking (a smoker was defined as smoking ≥ 1 cigarette/day for >1 year), menopausal status (postmenopausal was defined as ≥ 1 year without menstruation), and estrogen use (for >1 year).

Statistical analysis. Conditional logistic regression analysis for matched case-control groups was used to estimate the odds ratios (OR) and 95% confidence intervals (95% CI) for having radiographic features of hip OA per unit difference in standardized BMD of the femoral neck, total hip, lumbar spine, and total body. The standardized BMD reflects a normal distribution with a mean \pm SD of 0 ± 1 . BMI, lifetime physical activity, menopausal status, use of estrogen, and smoking were used as confounding variables for adjustment. BMI was entered as a continuous variable, and the rest were entered as categorical variables.

When a significant association between OA features and BMD was found, we estimated the intrapair differences in BMD in discordant twin pairs for different radiographic features of hip OA. Paired analysis was used; the twin with the radiographic feature of OA being treated was considered the case, and the cotwin was considered the control.

The analysis was carried out using the statistical software package STATA (Stata Corporation, College Station, TX).

RESULTS

Characteristics of the twins. Pelvic radiographs of 1,252 women (170 monozygotic [MZ] and 456 dizygotic [DZ] pairs) were assessed for features of hip OA. In 95% of the women, the nondominant hip was on the

Table 1. Characteristics of monozygotic (MZ) and dizygotic (DZ) twins*

	MZ (n = 320)	DZ (n = 828)	Total (n = 1,148)
Age, years, median (range)	55.5 (40–70)	52 (40–70)	53 (40–70)
Height, cm, mean \pm SD	161.48 \pm 5.8	162.68 \pm 5.3	162.35 \pm 5.5
Weight, kg, mean \pm SD	64.36 \pm 9.9	65.73 \pm 10	65.34 \pm 10
BMI, kg/m ² , mean \pm SD	24.68 \pm 3.6	24.84 \pm 3.7	24.79 \pm 3.6
Physically active, no. (%)	223 (76.4)	576 (72.0)	799 (73.2)
Ever smoker, no. (%)	151 (47.8)	416 (50.7)	567 (49.9)
Ever ERT user, no. (%)	124 (40.0)	306 (38.5)	430 (38.9)
Postmenopausal, no. (%)	234 (80.4)	517 (68.9)	751 (72.1)

* Percentages were calculated accounting for missing values for physical activity (56 missing values), smoking (11 missing values), estrogen replacement therapy (ERT; 43 missing values), and menstrual status (107 missing values). BMI = body mass index.

left side. To simplify the analysis, we included only twin pairs who both had complete bone mineral measurements at the left hip. Individuals with bilateral or left-sided hip replacement were excluded, as were their cotwins. The characteristics of the 1,148 twins (320 MZ and 828 DZ) included in the analysis are shown in Table 1. Slight differences between MZ and DZ twin pairs were seen for age and menopausal status, but this did not influence the intrapair analysis. Table 2 shows the characteristics of the twins' pelvic radiographs.

Informative twins were twin pairs discordant for a disease trait. Therefore, twin pairs discordant for overall hip OA and for the individual radiographic features of OPH and JSN were identified. Table 3 shows the discordant twin pairs when either hip joint was considered, as well as the twin pairs discordant for left hip OA only. As expected for a genetic trait, the percentage of discordant pairs was slightly higher in DZ versus MZ twins: 29% versus 23.1% for global OA grade, 23.7% versus 21.9% for OPH, and 14.3% versus 8.1% for JSN. There were fewer twin pairs discordant for radiographic features of left hip OA. The relationship was similar for JSN: 8.5% versus 5%, respectively, in DZ versus MZ twins.

Table 2. Prevalence of radiographic hip osteoarthritis (OA) characteristics in the twins*

	Either hip	Left hip
MJS, mm, mean \pm SD	3.3 \pm 0.8	3.3 \pm 0.7
MJS <2.5 mm, %	8	5
OPH \geq 1, %	14	9
OPH \geq 2, %	7	4
Sclerosis \geq 5, %	17	10
Global OA grade, %		
I	10	7
II	3	3
III	3	2
IV	1	<1
V	1	<1

* MJS = minimum joint space; OPH = osteophytes.

MZ and DZ twins were combined in the analyses. Table 4 shows the crude and adjusted OR for having radiographic features of left hip OA per unit difference in standardized BMD of the ipsilateral proximal femur.

OA and BMD at the ipsilateral hip. The (intrapair) risk (OR) of having radiographic left hip OA per unit difference in standardized BMD of the left femoral neck was 1.63 (95% CI 1.06, 2.50). The (intrapair) risk (OR) of having radiographic left hip OA per unit difference in standardized BMD of the left total hip was 1.42 (95% CI 0.95, 2.14). After adjustment for the possible confounding variables of BMI, lifetime physical activity, menopausal status, use of estrogen, and smoking, the risk per unit difference in standardized BMD of the left femoral neck remained elevated (OR 1.80 [95% CI 1.05, 3.12]), as did the risk per unit difference in standardized BMD of the left total hip (OR 1.55 [95% CI 0.90, 2.67]). It is possible that the control twin had radiographic features of right hip OA in a limited number of twin pairs. When these twins were excluded from the analysis (n = 20), results did not essentially change, with crude OR and 95% CI for having radiographic features of left hip OA remaining at 1.50 (0.97, 2.30) per unit difference in standardized

Table 3. Monozygotic (MZ) and dizygotic (DZ) twin pairs discordant for radiographic features of osteoarthritis (OA)*

	MZ twin pairs (n = 160)	DZ twin pairs (n = 414)	Total twin pairs (n = 574)
Either hip			
OA	37 (23.1)	120 (29)	157 (27.4)
Osteophytes	35 (21.9)	98 (23.7)	133 (23.2)
Joint space narrowing	13 (8.1)	59 (14.3)	72 (12.5)
Left hip			
OA	31 (19.4)	76 (18.4)	107 (18.6)
Osteophytes	28 (17.5)	61 (14.7)	89 (15.5)
Joint space narrowing	8 (5)	35 (8.5)	43 (7.5)

* Values are the number (%) of discordant twin pairs.

Table 4. Crude and adjusted odds ratios (OR) for having radiographic features of left hip osteoarthritis (OA) per unit difference in standardized bone mineral density (BMD) of the ipsilateral hip*

Standardized BMD	OA		Osteophytes		Joint space narrowing	
	n	OR (95% CI)	n	OR (95% CI)	n	OR (95% CI)
Femoral neck						
Crude OR	214	1.63 (1.06, 2.50)†	178	1.68 (1.05, 2.69)†	86	1.19 (0.61, 2.29)
Adjusted OR	172	1.80 (1.05, 3.12)†	138	1.70 (0.94, 3.08)	66	0.91 (0.35, 2.35)
Total						
Crude OR	214	1.42 (0.95, 2.14)	178	1.40 (0.91, 2.18)	86	0.99 (0.50, 1.98)
Adjusted OR	172	1.55 (0.90, 2.67)	138	1.41 (0.78, 2.57)	66	0.58 (0.20, 1.72)

* OR were adjusted for body mass index, lifetime physical activity, menopausal status, use of estrogen, and smoking. 95% CI = 95% confidence interval.

† $P < 0.05$ by conditional logistic regression.

BMD of the left femoral neck. Expressed as percent difference in BMD, twins with radiographic features of left hip OA had 3.3% (95% CI 0.5, 6.0) higher femoral neck BMD and 2.3% (95% CI -0.3, 5.0) higher total hip BMD than their unaffected cotwins (Table 5).

When the analysis was restricted to severe hip OA, the numbers of discordant pairs ($n = 24$) were too small for any realistic estimates.

Individual features of radiographic OA and BMD at the ipsilateral hip. The presence of left hip OPH was associated with increasing BMD at the left hip. Crude and adjusted OR and 95% CI for OPH were 1.68 (1.05, 2.69) and 1.70 (0.94, 3.08), respectively, per unit difference in standardized BMD of the left femoral neck (Table 4). The association was even stronger with severe osteophytosis of grade ≥ 2 OPH (crude OR 2.66 [95% CI 1.15, 6.15] and adjusted OR 3.32 [95% CI 1.03, 10.74] per unit difference in standardized BMD of the left femoral neck). Twin pairs discordant for the presence of left hip OPH had differences of 3.5% (95% CI 0.4, 6.6) in femoral neck BMD and 2.4% (95% CI -0.6, 5.3) in total hip BMD (Table 5). Twins with severe osteophytosis had 5.7% (95% CI 1.3, 10.0) higher femoral neck BMD compared with their unaffected cotwins.

Table 5. BMD differences in twin pairs discordant for OA and osteophytes at the left hip*

	BMD difference		
	Mean	%	95% CI
OA			
Femoral neck	0.0256	3.3	0.5, 6.0
Total hip	0.0212	2.3	-0.3, 5.0
Osteophytes			
Femoral neck	0.0275	3.5	0.4, 6.6
Total hip	0.0214	2.4	-0.6, 5.3
Severe osteophytes			
Femoral neck	0.0435	5.7	1.3, 10.0
Total hip	0.0232	2.6	-1.7, 7.0

* See Table 4 for definitions.

Radiographic OA and BMD at contralateral hips.

No clear association was found between left hip BMD and radiographic features of right hip OA. Crude and adjusted OR and 95% CI were 1.23 (0.84, 1.8) and 0.97 (0.58, 1.63), respectively, per unit difference in standardized BMD of the left femoral neck. If either twin had had left hip OA, this could have influenced the left hip BMD. We repeated the analysis excluding twins with left hip OA. As expected, the number of twin pairs discordant for right hip OA decreased ($n = 60$), but results remained essentially the same (crude OR 1.16 [95% CI 0.67, 2.00] per unit difference in standardized BMD of the femoral neck).

Radiographic hip OA and BMD at distal sites.

No clear association was found between the global OA grade in the worse hip, when either hip was considered, and either standardized BMD at the lumbar spine (crude OR 1.09 [95% CI 0.78, 1.53]) or whole body BMD (crude OR 1.19 [95% CI 0.84, 1.69]). There was no association of left hip OPH with BMD at the lumbar spine or total body.

Left hip JSN of any grade was not associated with BMD at any site.

Zygoty. When MZ and DZ twins were analyzed separately, the same trend was obtained (data not shown), but there was not adequate power to detect any difference between the groups due to insufficient numbers of discordant twins in each category.

DISCUSSION

This cotwin control study has confirmed the existence of an inverse relationship between OA and OP at the hip. Twins with radiographic features of hip OA had 3–4% higher BMD at the femoral neck area than their cotwins. However, the relationship was confined to the femoral neck and localized to the ipsilateral hip. There was no clear association of radiographic hip OA features with BMD in the contralateral hip, lumbar

spine, or total body. Of the individual features of OA, severe osteophytosis was associated with 5–6% higher BMD at the ipsilateral hip. There was no association with JSN. Adjustment for potential confounding variables such as BMI, lifetime physical activity, menopausal status, estrogen use, and smoking had no important effect on the results.

The association between OA and OP at the hip has been examined in previous studies (2,6,7,19–25). An inverse relationship has been found in most of them (2,6,7,19,20,22,24). In a few studies, however, no increase in bone density was seen in patients with hip OA (21,23,25). Earlier studies had small numbers (20,21) of hospitalized patients with total hip replacement as cases of OA (2,19–23). Such patients have symptomatic OA and are likely to have restricted mobility, which potentially affects bone mass. The investigators measured mainly cortical bone or used single-photon absorptiometry at the radius, or they used relatively crude measures of hip bone mass such as the Singh index (24). Few studies adjusted adequately for confounding variables.

Although there is still no clear consensus on how to define hip OA, plain radiographs of the pelvis offer the main basis of case definition for epidemiologic studies (26,27). The largest and most thorough study of hip OA and BMD to date was by Nevitt et al (6), who assessed pelvic radiographs of 4,855 subjects for individual radiographic features of hip OA and adjusted for anthropometric and other determinants of bone mass. Nevitt et al found that elderly Caucasian women with moderate-to-severe radiographic hip OA had higher BMD in the proximal femur (9–10%), spine (7%), and appendicular skeleton (3–5%) than women without hip OA, while women with bilateral hip OA and hip OA with OPH had a generalized increase in BMD. This contrasts with the comparatively lower percentage elevation in femoral neck BMD (3–4%) and the lack of association with lumbar spine and whole body BMD seen in the present study.

The use of the twin model might explain the difference. Our cohort consisted of MZ and DZ twins uniquely matched for age and closely sharing environmental and lifestyle factors. Although other studies adjusted for confounding variables, including age, residual confounding is still a potential problem. However, the main reason for the difference is likely to be the matching for genetic factors. MZ twins are genetically identical and DZ twins share an average of 50% of their genetic material. This suggests that much of the inverse relationship seen in previous studies is due to shared genetic factors between hip OA and high bone mass. These might be happening systemically through anthro-

pometric characteristics (9) and/or increased growth factor synthesis by osteoblasts (28), or locally at the joint level through increased bone metabolism (10).

Our results were site specific. The femoral neck area of the ipsilateral hip showed the highest BMD difference in twin pairs discordant for radiographic features of hip OA. This is similar to the finding reported by Nevitt et al (6), that BMD of the femoral neck was significantly higher in women with unilateral disease on the same side as the hip BMD scan, but not in the normal hips of women with OA on the contralateral side. This finding can be attributed to local subchondral bone remodeling. The changes in the bone architecture include increase in vascularity, venous congestion, marked increase in bone turnover with stiffening, and sclerosis of the bone resulting in trabecular hyperplasia (29–31). Radin and colleagues described the early stiffened subchondral bone in OA and gave a mechanical explanation of the observed changes in terms of a response of the bone to repetitive impulsive loading, as well as a repeated failure of the musculoskeletal peak dynamic force attenuation mechanisms (11,12). Others subsequently attributed the subchondral bone stiffness to a more general bone alteration (3), since increased skeletal concentrations of insulin-like growth factor 1 (IGF-1), IGF-2, and transforming growth factor β were found in osteoarthritic subjects (28). Recently, it has been shown that bone collagen metabolism is increased in osteoarthritic femoral heads, with the greatest changes occurring within the subchondral zone (10).

We also found a clear association of the presence and severity of OPH with higher BMD. This has been a constant finding in all recent, relevant, large studies (4–6). Even studies that showed coexistence of hip OA and generalized OP demonstrated that good bone formers, i.e., patients with hypertrophic OA, had an unusually low prevalence of spinal fractures and better bone quality in the histomorphometric analysis (25).

This is the first study to examine the relationship between hip OA and BMD at a number of sites while also adjusting for genetic factors and other confounding variables. Despite the large number of twin pairs included, there were limitations to the study. The number of discordant pairs was comparatively small, especially for MZ twins. Therefore, we pooled MZ and DZ twin pairs, with the results remaining essentially similar to those from DZ twin pairs alone. DZ twins, sharing an early common environment and 50% of their genetic material, are very similar compared with unrelated individuals in the general population. For the same reason, i.e., lack of statistical power, we were unable to

examine the relationship in severe cases of OA of global grade ≥ 3 . Another potential limitation of our study is the radiographic definition of OA, which is a problem in all epidemiologic OA studies (26,27). We used the Croft grading scale for global assessment, which has been used widely in epidemiologic surveys in the UK (17).

We also analyzed the individual radiographic features separately, this being subject to fewer limitations with less observer variation (17). Potential biases associated with twin studies generally include the generalizability of the study. As has been discussed elsewhere, the prevalence of radiographic OA in our twin population-based cohort was similar to that in the Chingford general population (16).

In conclusion, there is a small inverse relationship between radiographic findings of hip OA and femoral neck BMD on the affected side. Higher femoral neck BMD was especially associated with the presence and severity of OPH, but we found no evidence of a systemic increase in bone density. The stronger inverse relationship seen in previous studies, and a generalized increase in BMD in osteoarthritic subjects, may be attributed to shared genetic effects. This should prompt further investigations into identification of common genes for OA and bone formation that may be involved in the pathogenesis of the 2 common diseases and also local pathogenetic mechanisms that affect bone in OA.

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