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THE ASSOCIATION BETWEEN OSTEOARTHRITIS AND OSTEOPOROTIC FRACTURE: THE CHINGFORD STUDY

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SUMMARY

Studies of the association between the presence of osteoarthritis (OA) and the risk of osteoporotic fractures have produced conflicting results. To address this question further, we have examined the association between self-reported, validated fractures and radiological OA at multiple sites in a large population of normal Caucasian women aged 45–65 yr. Despite having increased bone mineral density (BMD) of 5.3%, subjects with hip OA had a significantly increased risk of fracture [odds ratio (OR) 2.38, 95% CI 1.06–5.35] compared to controls. Subjects with lumbar spine OA, however, had a significantly reduced risk of fracture (OR 0.45, 95% CI 0.23–0.80) compared to controls. This association was not explained by differences in BMD, weight, sex hormones or physical activity. No clear association was seen with fracture for hand or knee OA. These data suggest that the increased risk of fracture in subjects with OA of the hip is most likely to be due to mechanical and locomotor factors, such as the risk of falling.

KEY WORDS: Osteoarthritis, Fracture, Osteoporosis, Falls, Sex hormones, Validation.

OSTEOPOROSIS (OP) and osteoarthritis (OA) are two common age-related musculoskeletal disorders associated with considerable morbidity and mortality, which with an ageing population are likely to continue to increase in prevalence. For many years, an inverse association between OA and OP has been suggested. There is now considerable evidence from large population studies that patients with hip, knee and spinal OA have up to 15% higher bone mineral density (BMD) than controls [1–4]. However, the data for hand OA with or without generalized OA are less clear cut, with some studies showing a 6% increase in femoral neck BMD [4, 5], whilst others show no significant increase [6].

A more important issue to address is whether the increased BMD associated with OA is translated into a reduced risk of fractures. This was first suggested in a study showing that only 3/140 femoral heads excised due to fracture had evidence of OA [7]. Two population-based case–control studies of hip fracture and self-reported OA have shown that OA is associated with a reduced risk of hip fracture with odds ratios (OR) of 0.33 for hip OA and 0.48–0.78 for OA at any site, unexplained by differences in weight or body mass index (BMI) [8, 9]. One prospective study of self-reported OA failed to show any positive or negative association between OA and fractures including all sites, despite a 6% increased BMD, and suggested that this was due to an increased sway and reduced quadriceps strength [10]. A preliminary report of a prospective study of hip fracture and radiologically diagnosed hip OA has shown a non-significant increased risk of hip fracture in subjects with OA with an OR of 1.3, which on adjusting for calcaneal BMD increased to 2.6 [11].

The aim of this population-based case–control study was to examine the hypothesis that radiologically diagnosed OA decreases the risk of osteoporotic fracture. We also explore whether the association is mediated by weight, sex hormones, BMD or muscle strength.

METHODS

Subjects

From an age/sex register of a large general practice of >11 000 patients in Chingford, outer London, all 1353 women in the age range 45–64 yr (mean 54.2) were invited to participate in a study assessing musculoskeletal disease in the population [4]. A total of 1003 women were examined; six died, 66 had moved away and 278 refused or did not respond. This gave a crude response rate of 74% and an adjusted rate of 79%. Women from this general practice are similar to the UK general population in terms of weight (67 *vs* 65 kg), height (162 *vs* 161 cm) and BMI (25.6 *vs* 25.4 kg/m^2) [12]. All the women lived within 5 miles of the general practice and 98% of the women were white. A socioeconomic profile was performed using the Acorn classification system, which is based on each subject's postcode and residence (CACI International, London). These codes were linked to one of four socioeconomic categories. The women were predominantly middle class, but with a range of all social groups: 32% A/B, 42% C1, 17% C2 and 8% D/E.

All women completed a nurse-administered questionnaire including questions on all of the major risk factors for OP and OA, medical history, drug history, family history and physical activity. They also had basic anthropomorphic measurements taken, including height, weight, grip strength, and hip, waist and thigh circumference. BMD was measured at the lumbar spine

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(L1–L4) and at the femoral neck by dual-energy X-ray absorptiometry (DXA) using a Hologic QDR 1000 machine. In our hands, this machine has a reproducibility of 0.6–1.6%. Serum sex hormones oestradiol, sex hormone-binding globulin (SHBG) and dehydroepiandrosterone sulphate (DHEAS) were analysed in serum drawn at this visit.

Definition of osteoarthritis

OA was classified radiologically using standard X-rays of the pelvis, thoracolumbar spine, hands and weight-bearing knees. Radiographs were scored blind to the clinical details according to the methods of Kellgren and Lawrence (K and L), using the atlas of standard radiographs, by a single trained observer [13]. An individual was considered to have radiographic OA of the knee and first carpometacarpal joints (CMC) if at least grade 2 K and L was present on either side. Hand OA was considered to be present if the individual had either proximal and distal interphalangeal joint OA (PIP and DIP): for each site, 2+ changes had to be present in two or more joints to be considered positive.

X-rays of the thoracic and lumbar spine were graded for OA on a 0–3 scale for the presence of osteophytes: 0 = none; 1 = minimal; 2 = definite; 3 = severe. Lumbar and thoracic spine OA (LSOA and TSOA) were defined as those graded 1+ for each region [14]. OA of the hip was graded on a scale of 0–3 for the presence of femoral osteophytes: 0 = none; 1 = minimal; 2 = definite; 3 = severe. They were also graded for joint space narrowing according to the method of Croft [15]: a minimum joint space of $\leqslant$2.5 mm being defined as narrowing. Hip OA was defined for this study as those graded 1+ for femoral osteophytosis or the presence of joint space narrowing. The reproducibility of these grading techniques was good with kappa scores for inter- and intra-observer agreement ranging from 0.46 to 1.0.

Ascertainment and validation of fractures

During the nurse-administered interview, patients were asked details about fractures sustained in the previous 10 yr, including the site of the fracture, the date and whether it occurred during a road traffic accident (RTA). To validate these self-reported fractures, the general practitioners' notes were examined for all subjects reporting fractures and for 50 randomly selected subjects who did not report a fracture. Fractures were classified as: (i) definite if the notes contained an X-ray report or a direct reference to it in a letter from the orthopaedic or casualty department; (ii) probable if a fracture was mentioned in hospital letters or GP records, but without direct reference to the result of the X-ray; (iii) possible if the diagnosis was made purely on clinical examination; and (iv) not validated if there was no mention of the fracture in the notes.

All patients reporting a past history of fracture were sent a postal questionnaire requesting details of the circumstances surrounding the fracture, particularly about RTAs and falls from a raised object, in order to exclude traumatic fractures. Fractures were classified as traumatic if they occurred during an RTA, during a fall from the height of a chair or greater, or down a flight of stairs, and possible if they had fallen down 1–3 stairs.

Past vertebral fractures were ascertained by examination of the thoracic and lumbar X-rays using a validated algorithm, which used standard deviation cut-offs of anterior and posterior height [16]. A fracture was defined as at least two 2 S.D. deformities or one 3 S.D. deformity. As the majority of vertebral fractures are asymptomatic, it was not possible to perform a trauma questionnaire accurately. All vertebral fractures were assumed to be non-traumatic.

For our analysis, definite osteoporotic fractures were classified as: all past vertebral fractures without a definite history of trauma; all validated past fractures (probable or definite) with no or possible trauma.

Analysis

The baseline data of the case and control groups were compared by an unpaired t-test for normally distributed variables and by a Mann–Whitney U-test for non-parametric variables. Categorical variables were analysed using a χ^2 test. For analysis of appendicular OA, all cases of site-specific OA were compared with a control group with no appendicular OA. When analysing thoracic spine OA, all subjects with thoracic spine OA were compared to all subjects without thoracic spine OA. The co-existence of lumbar spine OA was adjusted for in the regression analysis. The reverse was performed for lumbar spine OA. Multivariate analysis was performed using logistic regression in the STATA software package.

Several stages of multivariate analysis were performed. The first step was to obtain a stable model for determining the OR of fractures by OA status by including potential confounding variables. This model contained age, weight, oral contraceptive pill usage, hormone replacement therapy usage, smoking and alcohol use, menopausal status and menopause duration.

TABLE I
Clinical characteristics of 92 fracture cases and 847 controls

	Controls (n = 847)	Cases (n = 92)	P
Age (yr)	53.7 (6)	57.0 (6)	< 0.0001
Weight (kg)	66.7 (11.7)	67.9 (12.3)	0.33
Post-menopausal status (%)	487/708 (68.8)	72/81 (88.9)	< 0.0001
Years since menopause	7 (3–12)	9 (4–14)	0.01
Ever HRT use (%)	194/847 (22.9)	24/99 (26.1)	0.49
Ever OCP use (%)	304 (35.9)	19 (20.6)	0.003
Alcohol (%)	706 (83.4)	68 (73.9)	0.024
Smoking (%)	396 (46.8)	38 (41.3)	0.32
BMD hip (g/cm^2)	0.77 (0.12)	0.71 (0.11)	< 0.0001

Figures in parentheses represent S.D. for continuous variables and percentages for categorical variables.

HRT, hormone replacement therapy; OCP, oral contraceptive pill.

TABLE II
Clinical characteristics of 319 subjects with appendicular osteoarthritis and 618 controls with no appendicular osteoarthritis

	No OA ($n = 618$)	OA ($n = 319$)	*P*
Age (yr)	52.6 (5.8)	56.9 (5.8)	< 0.0001
Weight (kg)	65.8 (11.4)	69.2 (12.4)	< 0.0001
Alcohol (%)	522 (84.3)	250 (78.4)	0.02
Ever OCP use (%)	243 (39.3)	72 (22.6)	< 0.0001
Ever HRT use (%)	156 (25.2)	68 (21.3)	0.18
Postmenopausal status (%)	332 (62.5)	278 (85.4)	< 0.0001
Years since menopause	6 (3–10)	7 (4–12)	< 0.0001

Figures in parentheses represent S.D. for continuous variables and percentages for categorical variables.

The next stage of the analysis was to examine whether variables were potentially on the causal pathway of the association by adding them into the above baseline model and observing its effects on the OR between OA and fractures. The three potential models considered in turn were: femoral neck BMD; fat ratio, oestradiol, DHEAS and SHBG; grip strength and physical activity score.

This study, using 95 cases and 600 unmatched controls, had >80% power to detect an OR of 2 with a significance value of 0.05 assuming a prevalence of OA of >20% in the exposed group.

RESULTS

Validation study

There were 119 reported non-vertebral fractures on which validation was attempted. No notes were available on 33 of the subjects as they had moved surgeries or died since the start of the study in 1987. Of the 86 cases where notes were available, there were 48 definite fractures, 11 probable fractures, six possible fractures and 21 unvalidated fractures. We then examined the percentage of fractures validated by the site of fracture, with the following results: hip, 100%; wrist, 66.7%; feet, 66.7%; hands, 50%; ribs, 40%; nose, 25%. The notes of 50 subjects not reporting fractures were examined, of which eight subjects had either moved or died. Of the remaining 42 subjects, there were 41 records with no mention of fracture and one case of a possible fracture of the foot, although this occurred outside the period of interest.

All 119 subjects were sent a further postal questionnaire asking about the circumstances of their fracture. There was no reply from 38 of the subjects, predominantly because they had been lost to follow-up from the study. Of the remaining 81 subjects, the results of the questionnaire were as follows: 68 cases with no trauma, five with possible trauma and eight with definite trauma. After the two validation processes, we were left with 92 definite fractures, of which 41 were vertebral and 51 appendicular.

Principal study

The results of the baseline data for the 92 fracture cases and the 600 controls are shown in Table I. More of the fracture subjects were postmenopausal, they were older and had a lower BMD at the femoral neck. Less fracture patients had used the oral contraceptive pill and those that had, had used it for a shorter duration than controls. More fracture patients had used hormone replacement therapy, but this could reflect prescriptions for the treatment of OP. There were less subjects who drank alcohol regularly in the fracture group, but those that did drank more units per week than the controls. The prevalence of radiological OA in the whole population was 52.6% at the thoracic spine, 35.9% at the lumbar spine, 10.0% at the hip (7.3% for joint space narrowing alone and 3.7% for femoral osteophytes), 11.7% at the knee, 14.7% at the hand and 15.9% at the CMC. The associations of key variables with OA are shown in Table II. Compared to subjects without OA, those with OA at any site were significantly older and heavier. More subjects with OA were postmenopausal with a greater duration of menopause. Less of them drank alcohol or had used the oral contraceptive pill or hormone replacement therapy. Subjects with OA had a greater BMD, adjusted for age and weight, at the femoral neck [0.80 (S.D. 0.01) *vs* 0.76 (S.D. 0.005), $P = 0.05$] and at the lumbar spine [1.00 (S.D. 0.01) *vs* 0.96 (S.D. 0.006), $P = 0.056$] compared to subjects with no appendicular OA.

Results of univariate and multivariate analysis are shown in Table III. On univariate analysis, all OA sites, with the exception of lumbar spine OA, were associated with an increased OR for fracture, with most sites achieving statistical significance. However, on multivariate analysis, only the associations with hip, thoracic and lumbar spine OA remained statistically significant, the associations at other sites disappearing. Further adjustments for BMD, sex hormones oestradiol, DHEAS, sex hormone-binding globulin, grip

TABLE III
Odds ratios (95% confidence intervals) for osteoarthritis and total validated fractures using univariate and multivariate analyses

Site of OA	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	OR adjusted for BMD	OR adjusted for sex hormones
CMC	1.5 (0.82–2.76)	1.0 (0.50–1.98)	0.87 (0.40–1.90)	1.10 (0.55–2.29)
Hand	2.19 (1.24–3.89)	0.87 (0.41–1.85)	0.78 (0.34–1.77)	0.85 (0.40–1.81)
Hip	2.38 (1.25–4.53)	2.38 (1.06–5.35)	2.75 (1.17–6.44)	2.39 (1.05–5.45)
Knee	1.95 (1.04–3.66)	1.03 (0.46–2.30)	1.07 (0.44–2.62)	1.01 (0.44–2.30)
Lumbar spine	0.65 (0.40–1.06)	0.45 (0.23–0.80)	0.45 (0.24–0.86)	0.45 (0.25–0.80)
Thoracic spine	1.63 (1.03–2.58)	1.73 (1.00–3.00)	1.98 (1.11–3.55)	1.74 (1.00–3.20)

Multivariate analysis is adjusted for age, weight, oral contraceptive pill usage, hormone replacement therapy usage, menopausal status, menopause duration, smoking and alcohol use. Adjustments for BMD and sex hormones are in addition to those in the multivariate model.

strength and physical activity had little effect on the OR. To assess possible differences in the type of OA, hip OA was subdivided into joint space narrowing and femoral osteophytes, giving adjusted OR of 1.80 (95% CI 0.53–6.07) and 3.62 (95% CI 0.66–19.9), respectively. Confining the analysis to association between vertebral fractures and vertebral OA, adjusted OR of 0.46 (95% CI 0.21–0.99) for lumbar spine and 3.57 (95% CI 1.55–8.24) for thoracic spine OA were obtained.

The data were re-analysed using more stringent criteria for the diagnosis of spinal OA: lumbar spine OA being defined as a total osteophyte score of 2+ (two vertebrae with a score of one or one vertebra with a score of two or more) and thoracic spine OA as a total vertebrae score of 6+. The prevalence of OA with this grading was 21% at the lumbar spine and 16.3% at the thoracic spine. The OR for the association with fractures, adjusted for confounding variables, were virtually unchanged: thoracic spine 1.60 (95% CI 0.84–3.04), lumbar spine 0.49 (95% CI 0.24–0.99).

DISCUSSION

These data do not support the hypothesis that the increased BMD associated with OA leads to a reduced risk of osteoporotic fracture, the exception being lumbar spine OA where there was a significantly reduced OR of fracture. All other sites were associated with an increased risk of fracture. However, on multivariate analysis, only the association with hip and thoracic spine OA remained statistically significant. The association between spinal OA and fracture remained strong and statistically significant when restricting the analysis to vertebral fractures, despite the reduction in statistical power of this analysis. The results for hip OA are consistent with a preliminary report by Nevitt *et al.* [11], the only other study to have used radiologically diagnosed OA, in a nested case–control study of 178 elderly women with an incident hip fracture and 1429 controls from the study of osteoporotic fractures. A 7% increase in femoral neck BMD in cases of OA was found. Despite this, the OR for fracture in cases with OA was 1.3 (95% CI 0.8–2.1) after adjusting for age, height, weight and strength. After adjusting for femoral neck BMD, the OR increased to 2.6 (1.3–5.3) and to 1.6 (0.95–2.6) after adjusting for calcaneal BMD.

Our results are at odds, however, with those of Cumming and Klineberg [8] and Dequeker and Johnel [9], who both reported the results of large population-based case–control studies with OR of 0.33 and 0.64, respectively. There are several important differences in study design which may explain this discrepancy. Both studies looked exclusively at all-cause hip fracture, whereas our study contained all validated fractures, including only five hip fractures. Both studies adjusted their results only for age and sex, leading to potential residual confounding. More importantly, both used self-reported OA; Dequeker using self-reports of physician-diagnosed OA and Cumming self-reports of joint pain requiring referral to a physician. This would tend to select out cases who had severe and symptomatic OA whose resultant referral to a physician may lead to interventions or lifestyle changes which modify risk factors for fractures.

We used the method of Kellgren and Lawrence to score knee, CMC and hand OA as it is a validated, reproducible and traditional technique at these sites. However, it is unreliable at the hip and, therefore, a different atlas was used for this site and at the lumbar spine. We continued to use this combination of atlases to maintain consistency of scoring with our previous paper on OA and BMD in this population, thereby allowing a more direct comparison to be made. Previous studies have consistently shown a stronger association between OA defined by osteophytes and increased BMD, with a weaker or non-significant association between joint space narrowing and BMD. Until now, no study of fractures to date has examined this relationship in detail.

Our data demonstrated that both femoral osteophytes and joint space narrowing at the hip are associated with an increased risk of fracture. However, the association was stronger with femoral osteophytes than with joint space narrowing, although the difference between them did not achieve statistical significance. Moreover, the OR were not altered by adjusting for femoral neck BMD, suggesting that the differential effect of osteophytes and joint space narrowing are not mediated via BMD. This could imply that osteophytosis is associated with changes in bone quality that are not detected by simple bone densitometry, but which do affect bone fragility. Alternatively, the presence of osteophytosis could simply be a better marker of clinical OA in this relatively young population.

It is intuitively attractive that any association between OA and fractures is mediated via changes in BMD. There is consistant evidence for a positive association between OA and BMD from several studies, including a study based on this population [1–4]. As an increase in BMD is associated with a reduced fracture risk [17], one would therefore expect a reduced risk of fracture in patients with OA. This study demonstrates that with the exception of lumbar spine OA, the increased BMD associated with OA is not translated into a reduced risk of fracture. However, the association between lumbar spine OA and fractures is reduced when adjusting for lumbar spine BMD [0.45 (95% CI 0.23–0.80) to 0.58 (95% CI 0.31–1.05)], and the association between hip OA and fracture is increased when adjusting for femoral neck BMD, indicating that the increased BMD partially explains the reduced rate of fracture with lumbar spine OA and reduces the excess fracture risk associated with hip OA.

Body weight is an important risk factor for both OP and OA, and could therefore potentially explain the association [18, 19]. However, our study has demonstrated that adjusting for weight has no effect on the association. To further examine this, we have looked at the fat ratio and endogenous sex hormones and again found no association apart from a small

reduction in OR at the knee. All of these studies taken together would suggest that any association between OA and fracture is not mediated through weight, body fat or endogenous sex hormones.

Why do patients with OA not have a reduced risk of fracture despite an increased BMD? The most likely explanation is that they are less agile and are therefore more susceptible to falls, and may be less able to protect themselves from subsequent injury during a fall. There is support for this hypothesis from Jones *et al.* [10] who found that subjects with OA had weaker quadriceps strength and greater body sway, both of which are known to be independent risk factors for falls [20, 21]. Adjusting our data for grip strength and physical activity had little effect on the OR, arguing against them being important in the association between OA and fractures. However, grip strength is an imperfect surrogate for the more relevant quadriceps strength, and most exercise questionnaires are relatively imprecise in measuring lifetime physical activity, leading to potential residual confounding. Indirect evidence in support of the fall hypothesis comes from population-based studies which examined risk factors for falls in the elderly. These have confirmed that even on multivariate analysis, self-reported OA of the hip and knee were associated with an increased risk of falling [20–22]. However, there are little data on the risk of falling and either radiologically diagnosed OA or OA at other sites.

Why are hip and thoracic spine OA associated with an increased risk of fracture when lumbar spine OA is associated with a decreased risk? All sites of OA are associated with similar increases in BMD when compared to controls: 6.2% for hip OA and 6.3% for lumbar spine OA [4], making this unlikely to be the explanation. There were no significant differences in any other risk factor between lumbar spine OA and the other sites to account for the difference. One possible explanation is that unlike hip OA, lumbar spine OA is not associated with an increased risk of falling or that it is associated with less severe falls, although the evidence to support this hypothesis is lacking at present.

It is more difficult to explain the difference between lumbar and thoracic spine OA. The criteria used to define spinal OA were very sensitive, leading to a high prevalence of OA at both sites; however, re-analysis using more stringent criteria did not significantly affect the results. There are no significant differences in the associations of lumbar and thoracic spine OA with either the baseline clinical characteristics or with OA at appendicular sites. Furthermore, 63.7% of subjects are concordant for OA status at both spine sites using the original criteria and 75.8% of subjects using the more stringent criteria.

The fracture ascertainment from this study produced approximate rates of appendicular fracture (119/10 000 person-years) consistent with those from Rochester, Minnesota (120/10 000 person-years), for the age group 45–55 yr [23]. The data from the validation exercise confirm previous reports that in women of this age group there is a 20–25% over-reporting of fractures when using the self-reporting technique, but that there is negligible under-reporting [24]. Our data would suggest that the over-reporting is site specific with the greatest misclassification being at sites such as the nose and ribs, and the least for clinically important fractures such as the hip and wrist. The classification that we used may exaggerate the degree of over-reporting as it assumes that the absence of documentation of a fracture in the patient's general practice notes implies that no fracture occurred, whereas in reality fractures of the finger or nose may be treated in casualty with no correspondence ever reaching the patient's general practice notes.

Our study, being retrospective in design, is subject to potential limitations. The main limitation is that some of the variables measured in the study may have been modified as a result of the fracture. This is a possibility with hormone replacement therapy use, which was non-significantly greater in the fracture cases than the controls. However, it is very unlikely that a previous fracture will affect the presence of radiological OA. Selection bias is a potential problem with all case–control studies. This was minimized by using all cases and controls from a normal population cohort which had a good response rate of 79%. A non-response survey has shown the responders to be similar to the non-responders for a range of variables.

In conclusion, this study rejects the hypothesis that the increased BMD associated with radiological OA leads to a decrease in osteoporotic fracture, with the exception of the lumbar spine where the hypothesis was supported. The increased risk of fractures at the hip does not appear to be explained by physical activity, grip strength, weight, sex hormones or BMD. The most likely explanation for this increased risk would appear to be an increased risk of falling, although further study is required to prove this hypothesis directly.

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