

The Relationship of Bone Density and Fracture to Incident and Progressive Radiographic Osteoarthritis of the Knee

The Chingford Study

Deborah J. Hart,¹ Camille Cronin,¹ Maxine Daniels,¹ Tina Worthy,¹
David V. Doyle,² and Tim D. Spector¹

Objective. Investigators performing cross-sectional studies have reported small increases in bone mineral density (BMD) in subjects with osteoarthritis (OA). This study was undertaken to examine the association of bone mass with incident and progressive disease and to determine whether prior fractures influence the development of OA.

Methods. Eight hundred thirty women had repeat knee radiographs 48 months from baseline. All radiographs were graded on the presence or absence of osteophytes and joint space narrowing (JSN). Incident knee OA was defined as new disease in the 715 women without knee OA at baseline. Progression was a change of at least one grade in the 115 women with baseline knee OA. All women underwent bone densitometry of the lumbar spine and hip. Rates of subsequent incident OA were compared between fracture groups.

Results. The 95 women with incident knee osteophytes had significantly higher baseline spine BMD (1.01 gm/cm² versus 0.95 gm/cm², or 6.3%; $P = 0.002$) and significantly higher hip BMD (0.79 gm/cm² versus 0.76 gm/cm², or 3.9%; $P = 0.02$) than those without incident disease. For the 33 women whose osteophytes progressed, no difference was seen compared with non-progressors in spine BMD, but hip BMD was modestly reduced (−2.5%). The 81 women who had incident JSN

had nonsignificantly higher baseline spine BMD (3.0%), while no difference was seen for the 30 women whose JSN had progressed. For hip BMD, a nonsignificant increase was seen in those with incident JSN (1.3%), and a nonsignificant reduction was seen in those whose JSN progressed (−2.7%). One hundred forty-five women sustained peripheral fractures, mainly in the distal forearm (27.6%) and vertebrae (28.3%). Women with a peripheral fracture had a reduced risk of subsequently developing incident knee OA (odds ratio [OR] 0.30, 95% confidence interval [95% CI] 0.11–0.84). Although numbers were smaller, nonsignificant reductions in rates of incident OA were seen for those with distal forearm (OR 0.40, 95% CI 0.11–1.49) and vertebral (OR 0.20, 95% CI 0.07–1.61) fractures.

Conclusion. These results confirm that for women who develop incident knee OA, defined by osteophytes, BMD is higher and of a magnitude similar to that shown in cross-sectional studies. Low BMD at the hip appears weakly related to progression. Women with previous fractures have less chance of developing OA, independent of BMD status. Although the mechanism for this action is unclear, these results suggest a possible common role of bone turnover and repair in the early manifestations of OA.

Large epidemiologic studies have established that higher levels of bone mass are associated with osteoarthritis (OA) (1–5). These studies have focused on cross-sectional data, and little is known about whether increased bone density is also seen in subjects with incident and progressive disease.

One longitudinal study examined change in bone mineral density (BMD) over 3 years and showed that women with incident knee OA had high baseline BMD

Supported by the Arthritis Research Campaign.

¹Deborah J. Hart, PhD, Camille Cronin, Maxine Daniels, Tina Worthy, Tim D. Spector, MD, MSc, FRCP: St. Thomas' Hospital, London, UK; ²David V. Doyle, MD, FRCP: Whipps Cross Hospital, London, UK.

Address correspondence and reprint requests to Deborah J. Hart, PhD, Twin Research and Genetic Epidemiology Unit, St Thomas' Hospital, Lambeth Palace Road, London SE1 7EH, UK. E-mail: deborah.hart@kcl.ac.uk.

Submitted for publication April 10, 2001; accepted in revised form September 3, 2001.

and were unlikely to lose that high level. However, this study had a young population with low levels of incident disease (6). The Framingham Study examined this relationship with the development of incident and progressive OA and found that high BMD was associated with an increased risk of incident OA, but that it decreased the risk of progression of knee OA (7). Studies have explored whether this increase in bone mass and mechanism of bone production have any influence on the rates of osteoporotic fracture. A large case-control study of femoral neck fracture from the Mediterranean Osteoporosis Study (MEDOS) found that previously diagnosed OA subjects were protected from hip fracture (by 40% in women and by 60% in men) (8). This association with protection from fracture in OA subjects has been confirmed in other studies (9,10). However, another large epidemiologic study failed to find an association with fracture in any joint with OA, despite the OA subjects having significantly increased bone density (11). Similarly, early cross-sectional data from the Chingford Study failed to show a cross-sectional association of forearm and spine fracture with knee and hand OA, but did show an increased risk for fracture in subjects with hip OA (12).

In the large, prospective Study of Osteoporotic Factors (SOF), no reduced risk of subsequent osteoporotic hip fracture was seen in those with hip OA (13). A possible reason for this failure of an increase in BMD to translate to reduced fracture risk is that OA subjects may be inclined to have postural instability and to experience more falls (11,13). It may also be due to changes in bone turnover or bone quality that lead to fracture irrespective of bone density status. Nevertheless, fracture rates in OA groups are inconsistent, and, to our knowledge, no investigators have reported the risk of developing OA in subjects with previous fractures.

We report here on the association of subjects' baseline BMD with the development of incident and progressive knee OA, and also examine whether previous fracture influences the development of incident and progressive knee OA.

PATIENTS AND METHODS

Subjects. The study subjects were from the Chingford Study population. Baseline observations were made in 1988–1989, and this well-documented cohort of 1,003 women has been seen annually and described in detail previously (14,15). The response rate at initial recruitment was 78%.

At the baseline examination, bone density was measured at the lumbar spine (L1–L4) and femoral neck region in gm/cm^2 using dual x-ray absorptiometry (QDR 1000; Hologic, Waltham, MA). Reproducibility, expressed as a coefficient of

variation from duplicate measurements in healthy volunteers, was 0.8% at the lumbar spine and 1.6% at the femoral neck.

At both baseline and 48-month followup, all women completed a standardized, nurse-administered questionnaire on medical history for a number of known risk factors for knee OA and osteoporosis. Height and weight were also recorded. Details and duration of smoking and average number of cigarettes smoked per day were recorded. All women who were taking estrogen at the time of the first examination and who continued to take estrogen throughout the 48-month followup period were classified as current users of estrogen replacement therapy (ERT). Ex-users were those who had used ERT for at least 60 months, but not during the previous 12 months. Any ERT users from baseline who had stopped during the 48-month followup were excluded from analysis. Women were asked for details of any knee injury, and knee pain was assessed using the National Health and Nutrition Examination Survey definition of knee pain lasting for >1 month.

Definition of OA. At baseline, all women underwent an anteroposterior (AP) weight-bearing radiograph of the knees, taken in full extension by the same technician using the same equipment. Views were standardized with the back of the knees in contact with the cassette, the patella centered over the lower end of the femur, and the beam centered 2.5 cm below the apex of the patella, with a tube-to-film distance of 100 cm. Women were contacted 48 months later and invited for a repeat screening for knee OA; 868 women responded, 830 of whom underwent a repeat AP, extended-view, weight-bearing knee radiograph using the same equipment, technician, and methods as detailed at baseline, to try to maximize standardization. Paired films were read side by side by a trained examiner for the presence of knee osteophytes and joint space narrowing (JSN) for each knee compartment using a validated atlas on a 0–3 scale of severity (16), with grade 1 being the definite presence of osteophytes or JSN and classified as a case. Subjects were classified as having incident radiographic OA if they developed grade ≥ 1 osteophytes or JSN from grade 0 at baseline. Subjects were classified as having progressive OA if they developed grade ≥ 1 osteophytes or JSN from grade 1 at baseline. Baseline hand radiographs were also graded for OA using the same radiographic criteria for presence of distal interphalangeal joint osteophytes, and 53 subjects were subsequently identified as having hand OA, defined as having ≥ 2 fingers affected with osteophytes.

Reproducibility of grading. Reproducibility of the radiographic grading system was assessed using radiographs of 50 women (100 knees), with two observers reading the radiographs 2 weeks apart. Longitudinal reproducibility was assessed by having the most experienced observer read radiographs of 20 women (40 knees). Radiographs were first read with the observer blinded to time sequence, and were then read side by side. Kappa coefficients were calculated as a measure of intra- and interobserver agreement.

Assessment and validation of fracture. Detailed data were sought on all fractures and falls occurring over the duration of the study, up to the 48-month followup. Information was obtained between 1989 and 1993 by interview at each annual visit and by phone calls every 6 months to reduce poor recall. All fractures were validated using the general practitioner's notes, employing a standardized protocol used previously (12). Fractures were classified as 1) definite, from

radiograph report or hospital report; 2) probable, from hospital letter or practitioner notes; 3) possible, diagnosed from clinical examination by practitioner; and 4) nonvalidated, no mention of fracture in notes. When notes were untraceable, all fractures were coded as missing.

Vertebral fracture was diagnosed by automated morphometry using a previously described algorithm (17). Lumbar and thoracic spine radiographs were assessed from baseline and 4-year followup to establish prevalent and incident vertebral fractures. All fractures relating to obvious trauma and nonosteoporotic fractures (nose, toe, jaw, skull) were excluded from analysis.

Statistical analysis. Analysis compared mean and SEM BMD in gm/cm^2 and percent difference in BMD in women with incident knee OA with these variables in women with no OA. OA was defined by incident and progressive osteophytes and incident and progressive JSN as separate outcomes. Odds ratios (ORs) and 95% confidence intervals (95% CIs) were calculated for the risk of developing incident and progressive OA in women sustaining peripheral fractures compared with the risk in women without fractures. For continuous variables, analysis of covariance was used to adjust for confounders of age, height, weight, smoking, ERT, activity, falls, and baseline BMD, using the package SPSSpc (SPSS, Chicago, IL).

RESULTS

Of the 1,003 women at baseline in 1989, 135 were lost to followup in 1993, either from moving away ($n = 40$), having died ($n = 11$), or no longer wanting to participate ($n = 84$). Baseline radiographs for 38 women from the original sample could not be located, and these women were therefore excluded from followup since there was no way of comparing radiographs. Paired radiographs were therefore available for analysis for 830 women (83% of the original sample). Of these women, 115 had baseline OA and were studied for analysis of progression. Seven hundred fifteen paired radiographs of women without knee osteophytes at baseline and 644 paired radiographs of women without JSN at baseline were used for analysis of incident disease.

To examine whether the followup groups were different in terms of selection, the rates of baseline OA in responders and nonresponders (including those missing baseline radiographs) to followup were considered. Of the 830 women with paired radiographs, 88 had knee OA at baseline (10.6%), a frequency similar to that of the 20 nonresponders to followup (11.6%) who were similar in age and weight.

Reproducibility of the radiographic grading showed that intraobserver agreement was high for osteophytes ($\kappa = 0.88$) and JSN ($\kappa = 0.83$), but that interobserver agreement was only good for osteophytes ($\kappa = 0.69$) and moderate for JSN ($\kappa = 0.54$). Reproduc-

ibility for change in longitudinal radiographs yielded intraobserver agreements of $\kappa = 0.79$ for osteophytes and $\kappa = 0.70$ for JSN. Little difference in reproducibility was seen between blinded or side-by-side readings, and the main radiograph analysis was therefore performed with baseline and 48-month radiographs side by side.

Of 715 women with paired radiographs, 95 (13.3%) developed incident knee osteophytes within 4 years, an incident rate of 3.3% per year, and 81 of 644 women (12.6%) developed incident knee JSN (3.1% per year). Twenty women (2.8%) developed bilateral incident osteophytes within the same time period, and 41 (6.4%) developed incident bilateral JSN. Only 9 women (1.3%) developed both osteophytes and JSN, too few for accurate further analysis. Of the 115 women with baseline OA, only 33 (4% of the 830 women with paired radiographs) progressed to osteophytes after 48 months and 30 (3.6% of the 830 women with paired radiographs) had worsening of JSN.

Fractures occurred in 185 women (each with 1 fracture) between 1989 and the 48-month followup visit. Of those 185 women, notes were missing for 6 (3.2%) or had no mention of fracture for 16 (8.6%). Eighteen women (9.7%) had fractures related to trauma and not to bone density (e.g., fractures of the toe, nose, and jaw, or related to high-intensity trauma), and these fractures were excluded, leaving 145 women (78.4%) with fractures to validate. Of these 145 women, 129 (89%) had definite fractures, 4 (2.8%) had letters from the hospital, and 12 (8.3%) had a positive physician opinion after examination. Of the 145 validated fractures, the majority were of the distal forearm (40, or 27.6%) and vertebrae (41, or 28.3%). The remainder were of the hip (6, or 4.1%), lower limb and foot (30, or 20.7%), upper limb and hand (20, or 13.8%), and sternum (8, or 5.5%).

Table 1 shows the main characteristics of the 830 women with paired radiographs available, including those with baseline OA. The mean \pm SD age of the group at baseline was 54.1 ± 5.9 years; after 4-year followup it was 58.1 ± 5.9 years. Table 1 also shows the mean differences between the 95 women who had developed incident disease (defined by incident knee osteophytes) and the 620 women who remained disease free after 4 years. Women with incident knee osteophytes were significantly older, heavier by 4.8 kg (10.6 lb), slightly taller, more likely to report knee symptoms at baseline (30% versus 18%), and twice as likely to have radiographic hand OA at baseline.

Figures 1 and 2 show the mean and SEM BMD and percent difference in BMD for the lumbar spine and hip by incident and progressive knee OA. As shown in

Table 1. Characteristics of 830 women with paired radiographs, 95 women with incident knee OA, and 620 women with no disease*

	Total (n = 830)	Incident OA (n = 95)	No OA (n = 620)	P†
Age (years)	54.1 ± 5.9	55.3 ± 5.6	53.3 ± 5.9	0.003
Height (cm)	161.7 ± 6.1	162.9 ± 6.1	161.6 ± 6.0	0.05
Weight (kg)	66.7 ± 11.5	69.9 ± 12.7	65.1 ± 10.4	<0.001
BMI (kg/m ²)	25.5 ± 4.1	26.3 ± 4.5	24.9 ± 3.7	0.001
Weight at age 20 years (kg)	55.1 ± 8.0	57.4 ± 7.5	54.8 ± 7.9	0.003
Spine BMD (gm/cm ²)	0.96 ± 0.15	0.98 ± 0.17	0.96 ± 0.15	0.20
Hip BMD (gm/cm ²)‡	0.76 ± 0.12	0.77 ± 0.13	0.75 ± 0.12	0.31

* Values are the mean ± SD. OA = osteoarthritis; BMI = body mass index; BMD = bone mineral density.

† Significance of comparison of women with incident OA versus those with no OA.

‡ Measured at femoral neck.

Figure 1, spine BMD was 6.3% higher in women with incident knee osteophytes (1.01 gm/cm² versus 0.95 gm/cm²), and this increase was significant ($P = 0.002$). As shown in Figure 2, hip BMD was also significantly higher (3.9%) in women with incident knee osteophytes (0.79 gm/cm² versus 0.76 gm/cm²; $P = 0.02$). BMD was also higher in women with incident JSN at the knee, although this was not significant (3.0% higher at the spine [1.00 gm/cm² versus 0.97 gm/cm²] and 1.3% higher at the hip [0.77 gm/cm² versus 0.76 gm/cm²]). Progression of knee osteophytes and JSN did not differ between the groups for spine BMD (Figure 1). Subjects had reductions in hip BMD of 2–3% (0.77 gm/cm² versus 0.79 gm/cm² for those with progression of knee osteophytes and 0.72 gm/cm² versus 0.74 gm/cm² for those with progression of JSN) (Figure 2).

Table 2 shows the characteristics of 145 women with fractures compared with 596 women with no fractures. As expected, women with fractures were significantly older and had lower spine and hip BMD. They also had significantly more knee injuries and falls and significantly more hysterectomies, and more of them had

used ERT at least once, although the difference in ERT use was nonsignificant.

Table 3 shows risk of incident and progressive OA by fracture group. For all fractures validated by a radiograph report plus a letter or physician examination, there was a 70% reduction in the risk of developing incident osteophytes (OR 0.30, 95% CI 0.11–0.84). A similar reduction in this risk was seen in the site-specific subgroups (distal forearm fracture OR 0.40, 95% CI 0.11–1.49; vertebral fracture OR 0.20, 95% CI 0.07–1.61), although the confidence limits included unity and were therefore not significant. No difference was seen for incident knee JSN, except for a lower risk for forearm fracture, although this was based on small numbers. No differences were seen for progression of OA. However, the numbers were small, since there were only 33 progressors (4%) in the 830 women with paired radiographs.

A subanalysis was carried out to see if there was a trend toward protection with time of fracture. In women who sustained a fracture after their baseline assessment in 1989 and before incident osteophytes developed, the OR was 0.26 (95% CI 0.06–0.89), but in

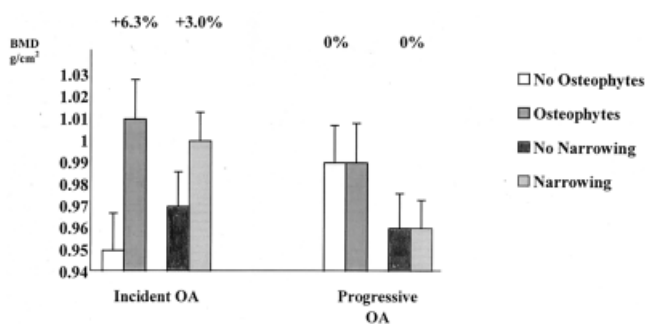
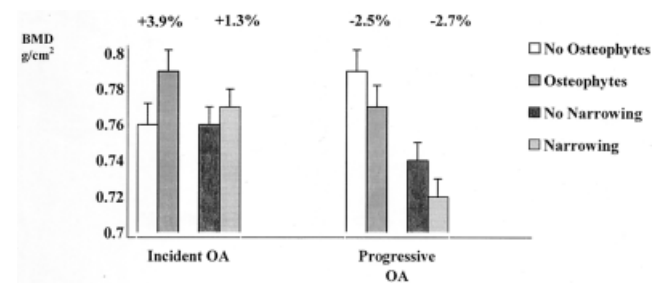
**Figure 1.** Mean and SEM bone mineral density (BMD) and percent differences in BMD for the lumbar spine, by incidence and progression of knee osteoarthritis (OA).**Figure 2.** Mean and SEM BMD and percent differences in BMD for the hip, by incidence and progression of knee OA. See Figure 1 for definitions.

Table 2. Characteristics of 145 women with recent fractures and 596 women with no fractures*

	No fractures (n = 596)	Fractures (n = 145)	P
Age, mean \pm SD years	53.6 \pm 5.8	55.6 \pm 6.1	<0.001
Height, mean \pm SD cm	161.9 \pm 6.0	161.3 \pm 6.2	0.27
Weight, mean \pm SD kg	66.7 \pm 11.8	67.3 \pm 10.3	0.54
Spine BMD, mean \pm SD gm/cm ²	0.99 \pm 0.15	0.90 \pm 0.15	<0.001
Hip BMD, mean \pm SD gm/cm ² †	0.77 \pm 0.12	0.72 \pm 0.11	<0.001
Hysterectomies, no. (%)	128 (21.5)	44 (30.3)	0.03
Knee pain, no. (%)	144 (24.2)	37 (25.5)	0.66
Knee injury, no. (%)	58 (9.7)	24 (16.6)	0.02
Ever used ERT, no. (%)	74 (12.4)	27 (18.6)	0.06
Ever smoked, no. (%)	265 (44.5)	64 (44.1)	0.99
Ever experienced falls, no. (%)	188 (31.5)	72 (49.7)	<0.001

* ERT = estrogen replacement therapy (see Table 1 for other definitions).

† Measured at femoral neck.

a group of 40 women who had sustained a fracture in the 10 years before baseline, the protective effect disappeared (OR 1.04, 95% CI 0.25–4.21). This suggests that recent fracture is more important than long-term fracture, although this finding is based on small numbers.

DISCUSSION

These data show that women with incident knee osteophytes had significantly higher BMD 4 years previously (by 6.3% at the lumbar spine and by 3.9% at the hip). Women with incident JSN at the knee also had a nonsignificant increase in BMD (3.0% at the spine and 1.3% at the hip). In women with progressive OA, no difference was seen for spine BMD compared with nonprogressors. Hip BMD was slightly lower (2–3%) in knee progressors. Women in this study who had sustained a recent fracture appeared to have a 70% reduced risk of developing incident knee OA. Adjusting for

potential confounders, such as baseline bone density, ERT, age, weight, height, falls, and physical activity, did not affect these results. Similar trends were also seen in women who had had distal forearm and vertebral fractures, although numbers in subgroups were small.

A number of studies have confirmed that an inverse relationship exists between bone density and OA, with OA subjects having significantly increased BMD (1–7). Previous cross-sectional data from the Chingford Study population found that OA subjects had a 6–9% increase in BMD (3). In the SOF, women with hip OA were found to have 8–10% higher spine and hip BMD (4). Investigators in the Rotterdam Study also found a 3–8% increase in BMD in OA subjects. Paradoxically, radiographic OA was also associated with elevated bone loss with age in men only (5).

All these studies focus on the development of prevalent OA, and few studies have looked at the association of BMD and OA longitudinally. A study examining change in BMD over 3 years as well as incident OA during that period showed that women with incident knee OA had high baseline BMD and were unlikely to lose that high level. That study differed from the present one in that it had a young population (age 28–48 years), and levels of incident disease were very low (6).

The only other study to examine longitudinal data was the Framingham Study, which examined the association of BMD with incident and progressive OA over an 8-year period. The study found that high BMD and BMD gain decreased the risk of progressive knee OA, but increased the risk of incident knee OA. That study's participants were older than those in the present study, and BMD was measured by different machines between the two time points (7).

This is the first prospective study to show the risk of incident and progressive OA following fracture. Investigators in a number of previous studies have exam-

Table 3. Risk of incident and progressive OA by fracture group*

	Patients with validated fractures (n = 133)†	Patients with validated fractures (n = 145)‡	Patients with distal forearm fractures (n = 40)	Patients with vertebral fractures (n = 41)
Incident osteophytes	0.34 (0.12–0.94)	0.30 (0.11–0.84)	0.40 (0.11–1.49)	0.20 (0.07–1.61)
Progressive osteophytes	0.74 (0.16–3.35)	0.65 (0.15–2.84)	0.36 (0.06–3.62)	NA
Incident JSN	0.93 (0.38–2.26)	0.95 (0.41–2.20)	0.18 (0.04–1.43)	0.67 (0.05–3.06)
Progressive JSN	1.54 (0.34–6.68)	1.54 (0.34–6.78)	1.49 (0.25–8.67)	NA

* Values are odds ratios (95% confidence intervals). All results are adjusted for age, height, weight, smoking, ERT, activity, falls, and BMD. NA = not available (numbers were too small); JSN = joint space narrowing (see Tables 1 and 2 for other definitions).

† Validated by radiograph report.

‡ Validated by radiograph report plus letter or physician examination.

ined the reverse scenario of risk of fracture in groups with already established OA to assess whether the increase in bone mass in OA protects against further fracture. The studies' findings are conflicting; investigators in the MEDOS reported that hip fracture was reduced by 40–60% in men and women with OA (8). Another study found that the prevalence of self-reported arthritis of the hip was much lower in patients with hip fracture (4%) than in controls randomly selected from the community (13%) (9). However, both of these studies relied on the unreliable diagnosis of self-reported OA (8) or self-reported arthritis (9). A study of hand OA and BMD in elderly women found that severe hand OA correlated with bone mass and that women with severe hand OA had fewer fractures (10).

In contrast to findings of these studies, an Australian study failed to find a reduced risk of osteoporotic fracture in men or women with self-reported OA, despite the fact that these subjects had 2–4.5% higher bone density. The authors concluded that lack of evidence for reduced fractures might have been due to subjects' postural instability and tendency to fall (11). Lack of consistent association with OA at different sites and fractures was also found by Arden et al (12) from previous data in the Chingford Study population. These investigators concluded that the increased risk of hip fracture might be due to falls related to immobility from OA. The SOF showed that despite having increased BMD, hip OA subjects had no reduction in vertebral fracture risk, although there was a trend toward reduced fracture risk in subjects with severe OA (13). The failure of increased BMD to translate to reduced fracture risk may be due to an increased number of falls sustained in patients with OA (18,19), or it may be related to depression (20).

Our study is subject to a number of potential limitations. This population consists of a group of middle-age to elderly white women, and results may not be generalizable to other groups. Furthermore, exact timing and age at fracture may have different consequences. Our study population has, however, been shown to be broadly representative of the population in the UK in terms of demographic variables. For example, statistics for this population are similar to those in the UK for women in the same age group in terms of height, weight, smoking, and rates of hysterectomy (21). It is possible to encounter selection bias for followup if only subjects with OA are willing to continue. However, in a large population with a good response rate for followup (83% of the original sample) and with mild disease, it is

unlikely that preferential selection would have altered the results to any extent.

In terms of definition of OA, results were inconclusive for progression of OA. Indeed, the numbers of women with progression were small. Only 4% had progressed in terms of osteophytes and 3.6% in terms of JSN. This left few subjects for meaningful analysis and resulted in low power; by examining the data at 10 years, it is likely that firmer conclusions could be drawn about the association of progression with fracture.

The timing of OA is always problematic. Our definitions are only as good as the sensitivity of the radiographs to early disease. It is possible that OA starts many years before radiographic changes are detected, and we have to be cautious about implying a temporal or causal relationship with fracture.

Equally interesting is the timing of the fracture. In reviewing our data, we looked at fractures occurring up to the development of incident disease. When we analyzed the timing of fracture, the group that experienced fracture from baseline had the same protective effect, but a small group of 40 subjects who had had fractures in the 10 years before baseline demonstrated no effect, suggesting that recent fracture is more important. This finding was based on small numbers, and it may be of interest to look at the temporal relationship of fracture and OA in larger studies.

If there is a real association between fracture and OA, why should a fracture be protective for OA independent of bone density? Any hypothesis at this stage is highly speculative. However, the repair mechanisms in bone may be involved, since bone scintigraphy shows increased bone activity for 12–18 months following fracture. It is possible that other biochemical and structural changes last longer and may have direct influences on growth factors, such as transforming growth factor β s (TGF β s), insulin-like growth factors, and bone morphogenetic proteins, which have an effect on bone and cartilage. After fracture, TGF β is released into the fracture site to initiate fracture repair and may be involved in cartilage metabolism (22). The role of factors such as endogenous TGF β in aiding the integrity of articular cartilage suggests a lessening of subsequent cartilage damage and therefore protection against OA (23). Preliminary data using an animal model suggest that TGF β may be essential in osteophyte formation and prevention of cartilage damage (24). However, whether these predominantly local factors can act systemically is at present unclear.

Post-fracture behavioral changes could result in less physical activity and a form of "joint protection."

However, we adjusted for lifelong physical activity and this made no difference to the results. It is unlikely that modest, short-term changes in behavior would be triggers for OA. Previously, in our data based on women, physical activity was only weakly associated with OA and probably could not have explained the results. BMD may have been altered following fracture, although we adjusted for baseline BMD, and this did not affect the results. Adjusting for baseline BMD may not be ideal in looking at 4-year incident data, but the average rate of bone loss in this population is <1% per year, and any changes are not likely to have affected the results.

Drug intervention may also be a possible explanation for the association with fracture. The treatment of fractures with bisphosphonates may affect bone remodeling (25). However, at the time of followup in 1993, bisphosphonates were rarely used and the treatment of choice for the few subjects with fractures who received therapy was estrogen.

Genetics also plays an important role in both OA and osteoporosis. We have previously demonstrated an association of the vitamin D receptor genotype with knee OA independent of bone density (26). This association has also been confirmed in other studies, and this genotype is also associated in some studies with propensity to fracture, suggesting a common genetic mechanism (27,28).

In conclusion, these data have shown that small, although significant, increases in spine and hip BMD are associated with incident knee osteophytes. Low hip BMD may be associated with progression of OA, although it is unclear whether this is cause or effect. Women with a recent history of fracture appear to be protected against developing radiographic OA regardless of age or ERT and bone density status. The mechanisms for this observation are unclear and may involve a combination of behavioral lifestyle changes and genetic factors. Overall, the results suggest that changes in bone metabolism may play an important role in the pathogenesis of OA.

ACKNOWLEDGMENTS

We thank the staff and patients of Highams Park Medical Partnership and Chingford Hospital. We also thank Dr. Eugene McCloskey for identifying vertebral fractures and Dr. Richard Keen and Dr. Nigel Arden for their assistance in fracture ascertainment.

REFERENCES

1. Cooper C, Cook PL, Osmond C, Fisher L, Cawley MI. Osteoarthritis of the hip and osteoporosis of the proximal femur. *Ann Rheum Dis* 1991;50:540-2.
2. 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.
3. Hart DJ, Mootosamy I, Doyle DV, Spector TD. The relationship between osteoarthritis and osteoporosis in the general population: the Chingford Study. *Ann Rheum Dis* 1994;53:158-62.
4. Nevitt MC, Lane NE, Scott JC, Hochberg MC, Pressman AR, Genant HK, et al, the Study of Osteoporotic Fractures Research Group. Radiographic osteoarthritis of the hip and bone mineral density. *Arthritis Rheum* 1995;38:907-16.
5. Burger H, van Daele PLA, Odding E, Valkenburg HA, Hofman A, Grobbee DE, et al. Association of radiographically evident osteoarthritis with higher bone mineral density and increased bone loss with age: the Rotterdam Study. *Arthritis Rheum* 1996;39:81-6.
6. Sowers M, Lachance L, Jamadar D, Hochberg MC, Hollis B, Crutchfield M, et al. The associations of bone mineral density and bone turnover markers with osteoarthritis of the hand and knee in pre- and perimenopausal women. *Arthritis Rheum* 1999;42:483-9.
7. Zhang Y, Hannan MT, Chaisson CE, McAlindon TE, Evans SR, Aliabadi P, et al. Bone mineral density and risk of incident and progressive radiographic knee osteoarthritis in women: the Framingham Study. *J Rheumatol* 2000;27:1032-7.
8. Dequeker J, Johnell O. Osteoarthritis protects against femoral neck fracture: the MEDOS experience. *Bone* 1993;14:S51-6.
9. Cumming RG, Klineberg RJ. Epidemiological study of the relation between arthritis of the hip and hip fractures. *Ann Rheum Dis* 1993;52:707-10.
10. Marcelli C, Favier F, Kotzki PO, Ferrazzi V, Picot MC, Simon L. The relationship between osteoarthritis of the hands, bone mineral density, and osteoporotic fractures in elderly women. *Osteoporos Int* 1995;5:382-8.
11. Jones G, Nguyen T, Sambrook PN, Lord SR, Kelly PJ, Eisman JA. Osteoarthritis, bone density, postural stability, and osteoporotic fractures: a population based study. *J Rheumatol* 1995;22:921-5.
12. Arden NK, Griffiths GO, Hart DJ, Doyle DV, Spector TD. The association between osteoarthritis and osteoporotic fracture: the Chingford Study. *Br J Rheumatol* 1996;35:1299-304.
13. Arden NK, Nevitt MC, Lane NE, Gore LR, Hochberg MC, Scott JC, et al, the Study of Osteoporotic Fractures Research Group. Osteoarthritis and risk of falls, rates of bone loss, and osteoporotic fractures. *Arthritis Rheum* 1999;42:1378-85.
14. Hart DJ, Doyle DV, Spector TD. Incidence and risk factors for radiographic knee osteoarthritis in middle-aged women: the Chingford Study. *Arthritis Rheum* 1999;42:17-24.
15. Hart DJ, Spector TD. The relationship of obesity, fat distribution and osteoarthritis in women in the general population: the Chingford Study. *J Rheumatol* 1993;20:331-5.
16. Burnett S, Hart DJ, Cooper C, Spector TD. A radiographic atlas of osteoarthritis. London: Springer Verlag; 1994.
17. McCloskey EV, Spector TD, Eyres KS, Fern ED, O'Rourke N, Vasikaran S, et al. The assessment of vertebral deformity: a method for use in population studies and clinical trials. *Osteoporos Int* 1993;3:138-47.
18. Nevitt MC, Cummings SR, Kidd S, Black D. Risk factors for recurrent nonsyncopal falls: a prospective study. *JAMA* 1989;261:2663-8.
19. Campbell JA, Borrie MJ, Spears GF. Risk factors for falls in a community based prospective study of people aged 70 and older. *J Gerontol* 1989;44:112-7.
20. Whooley MA, Kip KE, Cauley JA, Ensrud KE, Nevitt MC, Browner WS, the Study of Osteoporotic Fractures Research Group. Depression, falls, and risk of fracture in older women. *Arch Intern Med* 1999;159:484-90.

21. Knight IEJ. The heights and weights of adults in Great Britain. Office of Population Census and Surveys. London: Her Majesty's Stationery Office; 1984.
22. Bolander ME. Regulation of fracture repair by growth factors. *Proc Soc Exp Biol Med* 1992;200:165–70.
23. Pujol J-P. TGF- β and osteoarthritis: in vivo veritas? *Osteoarthritis Cartilage* 1999;7:439–40.
24. Scarstuhl A, van der Kraan P, Vitters E, van Beuningen H, van der Berg W. In vivo inhibition of endogenous TGF-Beta activity reduces osteophyte size and cartilage proteoglycan content [abstract]. *Ann Rheum Dis* 2000;60:51.
25. Myers SL, Brandt KD, Burr DB, O'Connor BL, Albrecht M. Effects of a bisphosphonate on bone histomorphometry and dynamics in the canine cruciate deficiency model of osteoarthritis. *J Rheumatol* 1999;26:2645–53.
26. Keen RW, Hart DJ, Lanchbury JS, Spector TD. Association of early osteoarthritis of the knee with a Taq1 polymorphism of the vitamin D receptor gene. *Arthritis Rheum* 1997;40:1444–9.
27. Uitterlinden AG, Burger H, Huang Q, Odding E, Duijn CM, Hofman A, et al. Vitamin D receptor genotype is associated with radiographic osteoarthritis at the knee. *J Clin Invest* 1997;100:259–63.
28. Uitterlinden AG, Weel AE, Burger H, Fang Y, Duijn CM, Hofman A, et al. Interaction between the vitamin D receptor gene and collagen type I α 1 gene in susceptibility for fracture. *J Bone Miner Res* 2001;16:379–85.