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THE ASSOCIATIONS OF BONE MINERAL DENSITY AND BONE TURNOVER MARKERS WITH OSTEOARTHRITIS OF THE HAND AND KNEE IN PRE- AND PERIMENOPAUSAL WOMEN

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Objective. **To determine whether Caucasian women ages 28–48 years with newly defined osteoarthritis (OA) would have greater bone mineral density (BMD) and less bone turnover over time than would women without OA.**

Methods. **Data were derived from the longitudinal Michigan Bone Health Study. Period prevalence and 3-year incidence of OA were based on radiographs of the dominant hand and both knees, scored with the Kellgren/Lawrence (K/L) scale. OA scores were related to BMD, which was measured by dual-energy x-ray absorptiometry, and to serum osteocalcin levels, which were measured by radioimmunoassay.**

Results. **The period prevalence of OA (K/L grade ≥2 in the knees or the dominant hand) was 15.3% (92 of 601), with 8.7% for the knees and 6.7% for the hand. The 3-year incidence of knee OA was 1.9% (9 of 482) and of hand OA was 3.3% (16 of 482). Women with incident knee OA had greater average BMD (z-scores 0.3–0.8 higher for the 3 BMD sites) than women without knee OA ($P < 0.04$ at the femoral neck). Women with incident knee OA had less change in their average BMD z-scores over the 3-year study period. Average BMD z-scores for women with prevalent knee OA were greater (0.4–0.7 higher) than for women without knee OA ($P < 0.002$ at all sites). There was no difference in average BMD z-scores or their change in women with and without hand OA. Average serum osteocalcin levels were lower in incident cases of hand OA (>60%; $P = 0.02$) or knee OA (20%; P not significant). The average change in absolute serum osteocalcin levels was not as great in women with incident hand OA or knee OA as in women without OA ($P < 0.02$ and $P < 0.05$, respectively).**

Conclusion. **Women with radiographically defined knee OA have greater BMD than do women without knee OA and are less likely to lose that higher level of BMD. There was less bone turnover among women with hand OA and/or knee OA. These findings suggest that bone-forming cells might show a differential response in OA of the hand and knee, and may suggest a different pathogenesis of hand OA and knee OA.**

Osteoarthritis (OA) is a major chronic disease. It has been estimated to affect 1 in 10 people at age 50 and >1 in 2 people at age 75 (1). Likewise, osteoporosis (OP) is a highly prevalent condition that has been estimated to affect 1 woman in 5 by age 80 (2). Thus, OP and OA are both common conditions that are more likely to affect women than men. It is relatively unusual, however, to find both conditions in the same individual.

Early clinical comparisons showed that elderly persons undergoing resection of the femoral head to treat hip OA were much less likely to have evidence of bone loss than were elderly persons who had femoral neck fractures (3). Subsequent studies indicated that persons with OA of the knee or hip were more likely to have higher bone mass than normal subjects or subjects with OP (4–6), whereas patients with OA of the hand might not have greater bone mass (7–9). This suggests either a difference in the pathogenesis of hand and knee OA or a possible measurement artifact. (Greater bone width is associated with generalized OA, and the definition of bone mass uses bone width in the assessment of cortical area) (10). Thus, there is evidence

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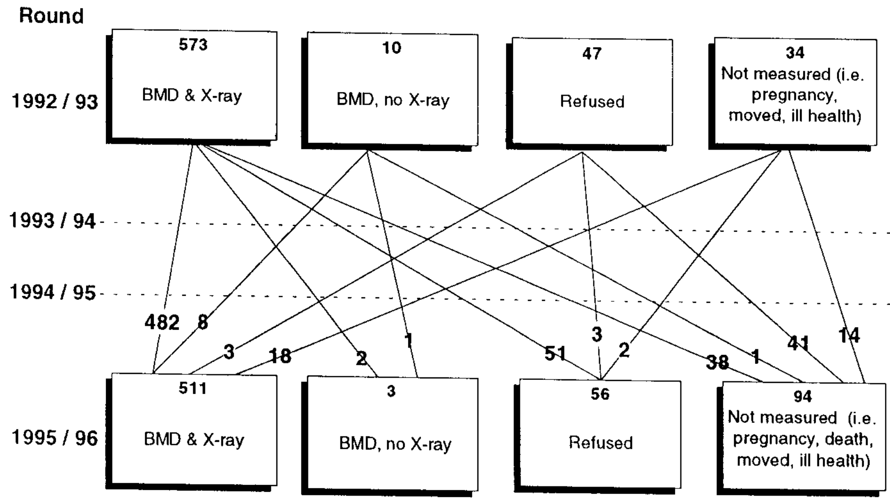

Figure 1. The status of the dynamic population in the Michigan Bone Health Study at the 1992/93 and 1995/96 examination rounds. BMD = bone mineral density.

that the pathogenesis of OA includes mechanisms related to skeletal calcification.

Hypotheses that have been proposed to explain a differential association between OA and OP have been primarily centered around responses to mechanical forces (11). It has been hypothesized that more stiff subchondral bone, as reflected by greater bone mass, increases cartilage damage with normal joint loading, and leads to the development of OA (11). However, there may be alternative explanations for the relative lack of overlap in the presentation of OA and OP, including genetic makeup (12), differences in response to changing ovarian hormone levels (13), or differences in other metabolic factors, such as vitamin D concentrations or growth factors (14–16). Finally, persons who present with OA may have a differential response of bone-forming cells over time (17). This may include enhanced osteoblast production and/or a mineralization deposition defect, as suggested by the presence of osteophytes and joint space narrowing in some cases with hip OA (18). Advancing our understanding of this apparent inverse relationship can enhance our understanding of the pathophysiology of each disease and the impact of selecting certain intervention measures.

We evaluated whether pre- and perimenopausal women with newly defined OA have increased bone mineral density (BMD). The purposes of this study were 1) to determine if pre- and perimenopausal women with OA have greater BMD, 2) to determine if there is less change in BMD among pre- and perimenopausal women with newly defined OA, and 3) to use longitudinal osteocalcin levels to determine if there is differential bone turnover in women with and without OA.

SUBJECTS AND METHODS

Study population. The Michigan Bone Health Study (MBHS) is a longitudinal study of arthritis and BMD in a dynamic cohort of Caucasian women in Tecumseh, Michigan. The MBHS was organized in 1988 to describe the natural history of peak bone mass, and 542 premenopausal women ages 20–40 years were recruited for participation. These initial enrollees represented >80% of the age-eligible female offspring listed in the family records of participants from the historical (1959–1960) Tecumseh Community Health Study (TCHS). In the ensuing 30 years, those 1960 TCHS family records no longer reflected all community residents. Thus, an additional 135 Caucasian women (who now lived in Tecumseh but whose parents had not been in the original TCHS) were contacted in 1992 by use of a population-based sampling frame and, of these, 122 were enrolled in the MBHS. This yielded 664 women (ages 25–45) who were eligible for participation in a population-based longitudinal study of musculoskeletal characteristics.

Of the 664 women (542 initial enrollees plus 122 later enrollees) who were eligible for participation in the 1992/93 OA study, 583 were measured for BMD; 81 did not participate (see Figure 1). Of these 81 nonparticipants, 47 refused, 19 were pregnant, 5 had severe health conditions, and 10 had moved from the area. Ten women with BMD measurements did not have radiographs.

This is a dynamic population, so women who had been pregnant, had refused participation, or had initially moved could return for annual examinations (see Figure 1). There were 602 women in the 1992/93 and/or the 1995/96 arthritis evaluations, but the denominator was 601 for the period prevalence, excluding 1 woman with rheumatoid arthritis. The denominator for the incidence estimate included 482 women with hand and knee radiographs and BMD measurements in both 1992/93 and 1995/96.

OA measurement. During the 1992/93 and 1995/96 annual examinations, anteroposterior (AP) radiographs were taken of the dominant hand and of both knees bearing weight. At both time points, films were taken by 1 of 3 trained and experienced technicians using General Electric radiographic equipment (model X-GE MPX-80; General Electric Medical Systems, Milwaukee, WI) and Kodak film (X-DA with Kodak rare earth intensifying screens; Eastman Kodak, Rochester, NY). The source film distance was 40 inches, and standard radiographic techniques were used.

Sixteen joints of the dominant hand and both knee joints (with weight bearing) were evaluated. Scoring was based on the Kellgren/Lawrence (K/L) grading system shown in the Atlas of Standard Radiographs of Arthritis (19). Each joint was classified according to a 5-point scale (0 = normal, 1 = doubtful OA, 2 = minimal OA, 3 = moderate OA, and 4 = severe OA) based on the degree of osteophyte formation, joint space narrowing, sclerosis, and joint deformity. Apart from the K/L criteria, joints were classified as unable to evaluate, missing, or showing changes consistent with rheumatoid arthritis.

Standardization of joint grading and evaluation of the consistency of grading between evaluators followed a multistep process. The readers reviewed the K/L grading criteria and evaluated films that were representative of all levels of OA (20). Then, 50 radiographs of knees and 50 radiographs of hands from the current study were evaluated independently by each reader, and their results were compared.

After completing standardization procedures, 2 readers (DJ, MCH, or MFS) independently evaluated and classified each joint from the 1995/96 radiographs and reread the 1992/93 films. For each joint, the scores assigned by the 2 readers were compared. Joints without perfect correspondence were reread and, if necessary, subjected to consensus reading. There were 18,086 joints with perfect concordance and 912 joints that required rereading and/or consensus evaluation. Kappa statistics indicated that agreement between the initial score and the consensus score was almost evenly divided between the 2 readers (21). A group of preselected films, representative of all levels of OA, were also dispersed throughout the study films and used to ascertain drift in different days of reading. There was no evidence of drift.

OA was defined as the presence of at least 1 joint with a grade of 2 or higher (in the hand and/or the knee). Women were defined as having hand OA if they had arthritis in any hand joint, and as having knee OA if they had arthritis in either or both knees.

BMD and osteocalcin measurements. BMD was measured annually at 3 sites (proximal femur, lumbar spine, and total body) using dual-energy x-ray absorptiometry (DXA; Lunar Corporation, Madison, WI). DXA uses a constant potential (76 kV[p] x-ray tube with K-edge filtration [350 mg/cm^2]) with effective beam energies at 38 keV and 70 keV. An individual woman's scanning speed was selected according to her AP abdominal thickness. Spine phantoms submerged in 15 cm or 25 cm of tepid water were evaluated at least weekly to assess drift over the 3-year period. There was no evidence of drift.

Table 1. Smoking, menstrual status, and alcohol consumption in pre- and perimenopausal women evaluated for the prevalence and incidence of osteoarthritis*

	Period prevalence (n = 601)	3-year incidence (n = 482)
Menstrual status		
Premenopausal	505 (84)	400 (83)
Postmenopausal	7 (1)	6 (1)
All others†	89 (15)	76 (16)
Smoking status		
Never smoked	400 (67)	324 (67)
Ex-smoker	69 (11)	56 (12)
Current smoker	132 (22)	102 (21)
Alcohol intake		
<30 gm/week	566 (95)	457 (95)
30+ gm/week	33 (5)	25 (5)

* Values are the number (%) of subjects.
† No longer menstruating (includes those with hysterectomy or double oophorectomy and those using hormone replacement therapy).

The BMD data are presented as z-scores based on comparison with the manufacturer's database (a z-score of zero is equivalent to the mean value in a young adult female population). Differences in BMD are the difference between the individual's z-score at baseline and the second BMD z-score at the 3-year followup assessment. This provides a comparable BMD value for the 3 bone sites whose absolute values are not comparable. Furthermore, BMD z-scores are now the standard approach used to delineate osteopenia and OP.

At annual examinations, blood was drawn during days 3–7 of the follicular phase of the menstrual cycle and after participants had been fasting for 8 hours. For women without menses, blood was drawn on the anniversary date of their first annual examination, while they were fasting. Serum was stored at −80°C, with no thawing and refreezing prior to assay for osteocalcin. Osteocalcin levels were measured using a radioimmunoassay (Incstar, Stillwater, MN) having an inter- and intraassay variation of <10%.

Other measurements. Table 1 shows the frequencies of the variables that characterize the women in the prevalence group and its subset, the incidence cohort. Two indicator variables were used to define 3 reproductive status groupings: 1) menstruating women who did not currently use hormone therapies were the reference group, 2) women without menstruation in the previous 12 months and without hormone replacement therapy, and 3) women with hysterectomy or oophorectomy, with and without hormone replacement therapy. Smoking behavior was described as never smoked, exsmoker, or current smoker. The mean (±SD) number of cigarettes smoked per day by current smokers was 18 ± 8.7, with a range of 1–40 cigarettes per day. Alcohol consumption was grouped as 1) women currently drinking <30 gm (<3 drinks) of alcohol per week, and 2) women currently drinking at least 30 gm of alcohol per week. Injuries were those that required a visit to the physician's office, and a qualitative description was used to gauge seriousness.

Recall of physical activity during the previous week, previous July, and previous December was recorded and averaged, and an algorithm modeled on the Stanford Five-City

Table 2. Means, standard deviations, and ranges describing the physical characteristics (measured in 1992/93) of Caucasian women evaluated for the prevalence and incidence of osteoarthritis

	Period prevalence (n = 601)		3-year incidence (n = 482)	
	Mean ± SD	Range	Mean ± SD	Range
Age, years	37.1 ± 5.0	25–46	37.4 ± 4.8	25–46
Weight, kg	71.5 ± 16.9	44–152	71.2 ± 16.8	44–151
Height, cm	163.4 ± 5.9	148–180	163.3 ± 6.0	148–180
Body mass index, kg/cm^2	26.8 ± 6.1	16.4–55.5	26.7 ± 6.0	16.4–54.1
Bone mineral density				
Total body, gm/cm^2	1.189 ± 0.072	0.702–1.497	1.190 ± 0.074	0.702–1.497
Lumbar spine, gm/cm^2	1.291 ± 0.153	0.866–1.297	1.291 ± 0.153	0.866–1.297
Femoral neck, gm/cm^2	1.016 ± 0.142	0.984–1.410	1.015 ± 0.142	0.984–1.410
Physical activity level (METS)*	340 ± 56	266–805	339 ± 53	266–778

* 1 METS = the energy consumed per minute of sitting at rest. See Subjects and Methods for details.

Study instrument (22) was used to indicate average weekly activity. The values were expressed in METS, with 1 METS being defined as the energy consumed per minute of sitting at rest. Height (in centimeters) and weight (in kilograms) were used to calculate the body mass index (BMI = weight [kg]/ height [m^2]). This study was approved by the University of Michigan Institutional Review Board.

Statistical analysis. Period prevalence of OA was defined using the cases identified in the 1992/93 study and the new cases in the 1995/96 examination. Incidence of OA was defined as the number of new cases identified in the 1995/96 evaluations from among the population still at risk for OA after the 1992/93 evaluation. The 95% confidence intervals (95% CI) were calculated for both the prevalence and the incidence.

Kappa statistics were calculated to quantify the extent to which the observed agreement between the 2 film readers exceeded that which would have been expected by chance alone. Because the percentage of agreement might be high due to the relative absence of women without radiographically defined OA, the percentage of agreement was calculated with only the number of women with OA as the denominator (21).

Univariate statistics were calculated for continuous variables, and frequency tables were developed for categorical variables. Analysis of variance models were developed to calculate the least squares mean BMD z-scores. BMD data are reported as z-values related to the "young adult women" level and adjusted for covariates, including age, body size, smoking, and injury, with an analysis of covariance. The significance level was set as a 2-sided test using a nonparametric approach (Wilcoxon). Logistic regression analysis was used to consider whether the probability of having (prevalence) or developing (incidence) OA was still related to BMD or its 3-year change after adjusting for covariates such as BMI, smoking, METS of physical activity, previous injury, or menstrual status.

RESULTS

The overall period prevalence of radiographically defined OA was 15.3% (92 of 601; 95% CI 12–18%), and the overall 3-year incidence of radiographically defined OA was 5.2% (25 of 482; 95% CI 3–7%). Of the 92 women with OA, 74 had grade 2 and 18 had grade 3 or 4 disease. This OA primarily reflects osteophytosis. Table 2 shows the means (±SD) and ranges for age, BMI, BMD, and physical activity levels among those included in the prevalence and incidence estimates.

OA of the knee. The period prevalence of radiographically defined knee OA was 8.7% (52 of 601; 95% CI 6–11%). The 3-year incidence of knee OA was 1.9% (9 of 482; 95% CI 0.7–3.0%). There were 48 women with grade 2 OA and 4 with grade 3 or 4 OA.

The mean 3 BMD z-scores (femur, spine, total body) of the prevalent cases of knee OA were greater (z-scores <0.5 higher) than the mean BMD z-scores of women without knee OA ($P < 0.0001$, 0.001, and 0.002 for the femoral neck, lumbar spine, and total body, respectively). These z-score differences remained statistically significant after adjusting for age, BMI, smoking, injury, and menstrual status. The three 1995/96 BMD z-scores remained similar to their 1992/93 BMD z-scores in women with knee OA (Table 3), whereas the 1995/96 BMD z-scores were lower in women without knee OA, which indicates bone loss over the 3-year period. This was statistically significant for the lumbar spine ($P <$ 0.03).

The average osteocalcin levels were 15% lower in prevalent cases of knee OA than in women without knee OA, suggesting less bone turnover ($P < 0.14$). The mean 3-year change in osteocalcin concentration was lower in prevalent cases of knee OA. Again, this suggests that there was less bone turnover in women with knee OA.

Incident knee OA. Incident cases of knee OA had BMD z-scores that were 0.8, 0.7, and 0.3 SD greater than the BMD z-scores of women without knee OA at the femoral neck ($P < 0.04$), lumbar spine ($P < 0.09$), and

Table 3. BMD z-scores (LS mean ± SE and range) and their changes and serum osteocalcin levels and their 3-year changes, according to the presence or absence of prevalent radiographically defined OA of the knee*

	With knee OA (n = 52)		Without knee OA (n = 549)		
	(LS mean ± SE)	Range	(LS mean ± SE)	Range	*P*†
Age in 1995/96, years	41.6 ± 0.7	28, 49	39.7 ± 0.2	28, 49	<0.01
BMD in 1992/93, z-scores					
Femoral neck	0.88 ± 0.17	−2.4, 4.2	0.16 ± 0.05	−2.1, 3.9	<0.0001
Lumbar spine	1.30 ± 0.19	−2.2, 4.9	0.68 ± 0.06	−1.8, 4.9	<0.001
Total body calcium	1.16 ± 0.13	−1.8, 3.9	0.72 ± 0.04	−1.7, 3.4	<0.002
3-year BMD change, z-scores					
Femoral neck	0.004 ± 0.06	−0.09, 0.87	−0.09 ± 0.02	−0.80, 0.87	<0.12
Lumbar spine	0.09 ± 0.05	−0.56, 1.29	−0.023 ± 0.02	−0.62, 1.09	<0.03
Total body calcium	−0.0002 ± 0.04	−0.31, 0.97	−0.02 ± 0.01	−0.79, 0.41	<0.06
Osteocalcin, ng/ml	1.61 ± 0.18	0.11, 5.2	1.92 ± 0.05	0.19, 5.8	<0.14
3-year osteocalcin change, ng/ml	−0.03 ± 0.19	−1.28, 6.8	0.38 ± 0.06	−2.5, 3.0	<0.07

* z-scores of young normal subjects reflect the manufacturer's normative database for Caucasian women. A z-score of zero represents the median value of the distribution of young adult women (adjusted for age, smoking, body mass index, and injury). BMD = bone mineral density; OA = osteoarthritis; LS = least squares.
† Based on Wilcoxon's 2-sample test.

total body ($P < 0.31$), respectively (Table 4). Furthermore, incident cases of knee OA were more likely to retain the same BMD z-scores in 1995/96 (shown in Table 4 as a positive number in the 3-year BMD z-score change), whereas the BMD z-scores for women without knee OA tended to drop.

The average osteocalcin levels were ~20% lower in incident cases of knee OA, but this difference was not statistically significant. Over the 3-year period, on average, bone turnover activity in women with knee OA declined (−0.60 ng/ml). However, bone turnover activity in women without knee OA tended to be greater over the 3-year period (+0.40 ng/ml).

OA of the hand. The period prevalence of radiographically defined hand OA was 6.8% (41 of 602; 95% CI 5–9%). The average age of women with prevalent hand OA was 43.8 years, compared with 39.5 years in women without hand OA ($P < 0.0001$). There was no difference in the BMI among women with and without hand OA.

The 3-year incidence of hand OA in these women was 3.3% (16 of 481; 95% CI 2–5%). Of the 41 women with hand OA, 13 had grade 2 and 18 had grade 3 or 4 disease. The average age of women with incident hand OA was 44.2 years, compared with 40.2 years in women without hand OA.

Table 4. BMD z-scores (LS mean ± SE and range) at 3 sites and their 3-year changes as well as osteocalcin levels and their 3-year changes, according to the presence or absence of incident (3-year) radiographically defined OA of the knee*

	With knee OA (n = 9)		Without knee OA (n = 473)		
	(LS mean ± SE)	Range	(LS mean ± SE)	Range	*P*†
Age in 1995/96, years	41.1 ± 1.6	28, 49	40.3 ± 0.2	28, 49	<0.55
BMD in 1992/93, z-scores					
Femoral neck	1.01 ± 0.40	−2.0, 4.2	0.19 ± 0.06	−2.1, 3.1	<0.04
Lumbar spine	1.41 ± 0.43	−2.0, 4.2	0.71 ± 0.06	−1.74, 3.2	<0.09
Total body calcium	1.07 ± 0.31	−1.8, 3.9	0.76 ± 0.04	−1.3, 2.1	<0.31
3-year BMD change, z-scores					
Femoral neck	0.004 ± 0.13	−0.90, 0.97	−0.09 ± 0.02	−1.5, 1.42	<0.54
Lumbar spine	0.37 ± 0.11	−0.56, 1.30	−0.04 ± 0.02	−0.83, 1.85	<0.02
Total body calcium	0.04 ± 0.08	−0.31, 0.96	0.02 ± 0.01	−0.51, 1.04	<0.14
Osteocalcin, ng/ml	1.59 ± 0.40	0.11, 5.2	1.94 ± 0.06	0.55, 5.8	<0.53
3-year osteocalcin change, ng/ml	−0.60 ± 0.42	−2.28, 3.8	0.40 ± 0.06	−1.5, 3.0	<0.05

* z-scores of young normal subjects reflect the manufacturer's normative database for Caucasian women. A z-score of zero represents the median value of the distribution of young adult women (adjusted for age, smoking, body mass index, and injury). BMD = bone mineral density; OA = osteoarthritis; LS = least squares.
† Based on Wilcoxon's 2-sample test.

There was no difference in the mean BMD levels (as z-scores) or their 3-year change when comparing women with prevalent hand OA with women without hand OA. Likewise, there was no difference in the mean BMD levels (as z-scores) or their 3-year change when comparing women with incident hand OA with women without hand OA.

On average, women with hand OA (either prevalent or incident cases), had less active bone turnover. The average osteocalcin levels were 25–35% lower in both prevalent ($P < 0.007$) and incident ($P < 0.02$) cases of hand OA, a difference that persisted after adjusting for age, BMI, smoking, injury, and menstrual status.

Osteocalcin activity increased significantly in those women without hand OA (+0.41 ng/ml), whereas it declined in women classified as having incident hand OA (−33 ng/ml) ($P < 0.03$). This remained statistically significant after adjusting for age, BMI, physical activity, smoking, and menstrual status.

DISCUSSION

This is a longitudinal study of bone mineral density, bone turnover, and OA in women ages 28–48 years. Several studies have characterized factors associated with OA in late middle-aged and elderly populations (23–26). However, the risk factors identified in those prevalence studies of the elderly are not positioned to capture factors that precede the development of OA. This is particularly true when risk factor information, such as bone density or bone turnover, are unavailable in conventional health records and cannot be recalled by a respondent.

In this population-based study, we found that knee OA was associated with greater BMD, consistent with observations in older populations and in clinical populations. Furthermore, women with knee OA maintained or increased their BMD over a 3-year observation period compared with women without knee OA. This was observed even though women with knee OA were slightly older than those women without knee OA.

The measures of osteocalcin may provide the evidence of how these higher BMD levels may accrue. Women with knee OA and/or hand OA had lower bone turnover, as represented by cross-sectional osteocalcin concentrations, than did women without OA. Furthermore, women with knee OA and/or hand OA continued to have less bone turnover, as measured by osteocalcin levels over a 3-year period, than did women without OA.

This investigation builds upon previous work with osteocalcin as a marker of bone turnover (17,27,28). Dequeker et al (27) found more bone and higher levels of osteocalcin among women with hand OA and concluded that this represented a "stiffer" bone. Sharif et al (28) associated higher serum osteocalcin levels with late-phase bone scan abnormalities. Campion et al (17) suggested that higher levels of serum osteocalcin were found primarily in a small number of patients with a destructive OA, and lower levels of serum osteocalcin were observed in patients with nondestructive OA.

The decreased levels of serum osteocalcin present in these women who are in the process of developing OA suggest a differential response of bone-forming cells in those who have recently developed knee OA. However, bone turnover would be expected to increase if, over time, and in selected individuals, the OA process becomes increasingly destructive.

Because serum osteocalcin may represent the contribution from multiple skeletal sites, it is important to question whether serum osteocalcin levels are linked with osteocalcin concentrations in other tissues more proximal to the affected joints. Several studies have reported that serum osteocalcin and synovial fluid osteocalcin levels were correlated, albeit the absolute levels of osteocalcin were significantly lower in the synovial fluid than in the serum (29,30).

This study, based on data from incident cases, questions the paradigm that labels women who develop OA as "bone formers." That term suggests only an accelerated capacity to lay down bone. These women may indeed lay down more mineral or generate more matrix; however, simultaneously, an important element to now consider is that their bone cells may not be turning over as rapidly. This suggests that other factors, such as a less vigorous osteoclast behavior, differences in growth-promoting factors, or differential hormone control of the calcification process, must also be considered.

There are 2 reports which suggest that bone mass is increased in persons with OA, but that the rate of bone loss is greater in those with OA (9,31). There are several potential explanations. The bone loss could be associated with long-term chronic inflammatory processes because the sites measured for bone were also the sites of localized OA. This includes the cortical area associated with hand OA in the Sowers et al study (9) and hip BMD associated with OA of the hip in the Dequeker et al study (31). The difference could also be a phenomenon of age. The MBHS population is relatively young and premenopausal, while the other 2 studies (9,31) were of populations that were older and postmenopausal.

It is also important to address the limitations of the present study. First, serum osteocalcin concentrations reflect systemic concentrations whereas the OA measures are specific to the joints in the hands and knees. Bone turnover from the skeleton and bone in other joint sites could be major, but unmeasured, contributors to the serum osteocalcin levels. Second, while the woman with RA was eliminated from our analyses, OA as defined by the K/L scale is not a homogenous condition and any difference in bone turnover attributed to OA subsets is not identified in this study. Third, statistical power is still somewhat limited because of the relatively few incident cases.

In summary, these data indicate that women ages 28–48 years who have knee OA have greater BMD than women without knee OA and are less likely to lose that higher BMD level than are women without knee OA. Furthermore, osteocalcin levels indicate that there is less bone turnover in both hand OA and knee OA. These findings suggest that OA should also be defined as having a differential response of bone-forming cells with time, at least in pre- and perimenopausal women. This suggests that it is no longer adequate to evaluate OA risk in terms of BMD measures alone.

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