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Osteoporosis and Vitamin-D Deficiency Among Postmenopausal Women with Osteoarthritis Undergoing Total Hip Arthroplasty

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Commentary and Perspective, data tables, additional images, video clips and/or translated abstracts are available for this article. This information can be accessed at <http://www.ejbjs.org/cgi/content/full/85/12/2371/DC1>

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OSTEOPOROSIS AND VITAMIN-D DEFICIENCY AMONG POSTMENOPAUSAL WOMEN WITH OSTEOARTHRITIS UNDERGOING TOTAL HIP ARTHROPLASTY

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Background: Several epidemiological studies have shown a lower prevalence of osteoporotic hip fractures in patients with osteoarthritis. Other studies have demonstrated elevated bone mineral density in patients with osteoarthritis. The prevailing view is that there may be an inverse relationship between osteoarthritis and osteoporosis. The purposes of the present study were to describe a subgroup of patients with osteoarthritis who were found to have osteoporosis and to assess the vitamin-D status and other risk factors for low bone density in osteoarthritic subjects with and without osteoporosis.

Methods: The bone mineral density of the spine, the proximal part of the femur, and the total body was measured with dual-energy x-ray absorptiometry in sixty-eight postmenopausal white women who were scheduled to undergo total hip replacement for advanced osteoarthritis. The serum levels of 25-hydroxyvitamin D, 1,25-dihydroxyvitamin D, intact parathyroid hormone, osteocalcin, and bone-specific alkaline phosphatase and the urinary level of N-telopeptide were measured. Information from validated lifestyle, dietary, and demographic questionnaires was also evaluated.

Results: Seventeen (25%) of the sixty-eight women had occult osteoporosis (as indicated by a T score of less than -2.5). Fifteen (22%) of the sixty-eight subjects had vitamin-D deficiency, and three (4%) had an elevated serum parathyroid hormone level. Only two of the seventeen osteoporotic women had vitamin-D deficiency. On the basis of these numbers, vitamin-D status was not correlated with bone density ($p = 0.32$). Analysis of the relationship between the number of years since menopause and osteoporosis or markers of elevated bone turnover showed that osteoporosis was detected throughout the postmenopausal period.

Conclusion: A substantial portion of these sixty-eight white women with osteoarthritis of the hip had occult osteoporosis and hypovitaminosis D. Vitamin-D deficiency was not restricted to the group with low bone density. These results support the need to consider the presence of both osteoporosis and vitamin-D deficiency in women with advanced osteoarthritis.

Level of Evidence: Therapeutic study, Level III-1 (case-control study). See Instructions to Authors for a complete description of levels of evidence.

Osteoarthritis is a disease of cartilage, but it is associated with changes in bone tissue. Osteoarthritis is often characterized by radiographic evidence of osteosclerosis in subchondral bone and of osseous outgrowths, or osteophytes, in the affected joint. In contrast, osteoporosis is

characterized by a loss of bone mineral density that can be assessed with dual-energy x-ray absorptiometry. The diagnosis of osteoporosis can be made when the bone mineral density is reduced by 2.5 standard deviations below the mean value for young normal individuals¹. The relationship between these musculoskeletal diseases is of special relevance to the aging population because both diseases increase with age, although the impression is that they do not commonly occur together in the same patient.



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TABLE I Comparison of Osteoarthritic Women with and without Osteoporosis

	Osteoporotic* (N = 17)	Non-osteoporotic* (N = 51)	P Value
Age† (yr)	69 (65, 74)	65 (59, 70)	0.04
Years since menopause†	22 (16, 26)	16 (9, 22)	0.02
Z score†			
Femoral neck	-0.54 (-0.86, 0.21)	0.98 (0.33, 2.08)	0.00001
Trochanter	-0.65 (-1.09, 0.05)	1.10 (-0.10, 1.76)	0.00001
Weight† (kg)	63.5 (57.3, 65.8)	74.2 (66.7, 85.2)	0.0003
Body fat† (%)	45.1 (39.1, 48.7)	47.3 (42.1, 52.1)	0.09
Calcium intake† (mg/d)	700 (298, 1072)	880 (552, 1120)	0.20
Alcohol consumption† (drinks/wk)	1.0 (0.3, 3.5)	1.0 (0.0, 3.0)	0.84
Physical activity† (metabolic hr/wk)	19.6 (9.8, 40.8)	16.4 (5.8, 37.1)	0.60
Estrogen replacement†	53%	58%	0.78
Smoking† (pack-years)	0.0 (0.0, 2.5)	8.0 (0.0, 22)	0.05

*Osteoporotic subjects were those with a T score of less than -2.5, and non-osteoporotic subjects were those with a T score of at least -2.5.
†The data are presented as the median, with the lower quartile and upper quartile in parentheses. ‡The data are presented as the percentage of subjects with a history of estrogen replacement.

More than thirty years ago, Foss and Byers noted the absence of osteoarthritic changes on the radiographs of fractured hips in osteoporotic subjects². Although that was a retrospective study in which the subjects were not well-matched for age and gender, it was the basis for the view that osteoarthritis protects against hip fracture³. Subsequent studies with more fully characterized subjects showed associations for certain bones or certain subgroups⁴⁻⁸.

In a previous study that was designed to characterize women who presented for total hip arthroplasty following an acute osteoporotic hip fracture, postmenopausal women with osteoarthritis but without a fracture who were scheduled to undergo total hip arthroplasty were used as a control group⁹. An unexpected finding was that many of the osteoarthritic subjects had evidence of osteoporosis. In the present study, the subgroup of osteoarthritic women who had generalized osteoporosis at the time of total hip arthroplasty were compared with the subgroup of osteoarthritic women who did not. Because we previously found vitamin-D deficiency in women with osteoporotic fractures⁹, we tested whether vitamin-D deficiency was associated with osteoporosis in osteoarthritic women.

Materials and Methods

Subjects

The study group consisted of a group of osteoarthritic women who had been previously compared with women who had an acute hip fracture⁹. The study was approved by the prevailing Institutional Review Boards. Informed consent was obtained. Osteoarthritic women who were scheduled to undergo total hip arthroplasty were identified by monitoring the orthopaedic schedules at Brigham and Women's Hospital and New England Baptist Hospital. All subjects were postmeno-

pausal women who had experienced either natural or surgical menopause with amenorrhea for at least twelve months. Subjects were not included in the study if they declined to participate, if they had comorbid medical conditions or were taking medications (other than estrogen) that could affect bone mass, or if they had underlying hip disease other than osteoarthritis. Excluded comorbid medical conditions were renal insufficiency (as indicated by a creatinine level of ≥ 177 $\mu\text{mol/L}$), malabsorption, gastrectomy, active liver disease, acute myocardial infarction, alcoholism, and anorexia nervosa. A total of 543 potential subjects were contacted by mail with an invitation to submit an opt-in postcard. Of these, 374 women did not respond to our initial contact and 101 did not meet the inclusion criteria. The remaining sixty-eight women were enrolled in the study. Although it was not intended, all sixty-eight enrolled subjects were white. They ranged in age from forty-six to eighty-nine years.

Questionnaires

Using a modification of the Nurses' Health Study questionnaire¹⁰ as well as dietary and detailed physical activity¹¹ questionnaires, all participants provided information regarding lifestyle, reproductive factors, dietary calcium consumption, and physical activity (Table I).

Bone Density and Body Composition

The bone mineral density of the spine (from L1 to L4), the proximal part of the femur, and the total body were measured with use of dual-energy x-ray absorptiometry (QDR2000; Hologic, Bedford, Massachusetts). The in vivo precision (coefficient of variation percentage) of the bone density measurements for the spine, femoral neck, and trochanter in postmenopausal women on different days were 1.21%, 1.74%, and

1.24%, respectively¹². Bone density values for vertebrae with moderately severe osteoarthritic changes, disc-space narrowing, or a fracture were excluded from the analysis because those anatomical findings may falsely elevate the bone mineral density. The results were expressed as Z scores, i.e., the standard deviation from the mean value for age-matched normal women. Body composition (lean and fat mass) was determined with use of dual-energy x-ray absorptiometry. The ratio of fat tissue to lean tissue was calculated. The mean reproducibility (and standard error of the mean) for fat and lean tissue determinations in our laboratory were 1.09% ± 0.15% and 0.89% ± 0.28%, respectively.

Blood-Chemistry

Studies and Assays

Blood-chemistry studies, complete blood-cell counts, and tests of urinary calcium levels were performed. Blood samples were obtained preoperatively. Serum 25-hydroxyvitamin-D levels were measured with use of a radioimmunoassay procedure (Incstar, Stillwater, Minnesota) that has been approved by the Food and Drug Administration. Its sensitivity is 2.2 ng/mL, and the intra-assay and interassay coefficients of variation as determined in our General Clinical Research Center laboratory were 8.7% and 12.1%, respectively. Vitamin-D deficiency is defined as a 25-hydroxyvitamin-D level of <37.5 nmol/L^{13,14}. Levels of 1,25-dihydroxyvitamin D were measured with the radioimmunoassay procedure, and the intra-assay and interassay coefficients of variation were <8% and 9%, respectively. Serum intact parathyroid hormone levels were measured with the sensitive Allegro immunoradiometric assay (Corning Nichols Institute, San Juan Capistrano, California). The detection limit is 1 pg/mL, and the intra-assay and interassay coefficients of variation as determined in our laboratory were 5.0% and 2.5%, respectively. Urinary N-telopeptide levels, an index of bone resorption, were determined in a

twenty-four-hour urine collection with use of an enzyme-linked immunosorbent assay that measures cross-linked collagen peptides (Osteomark Assay; Ostex International, Seattle, Washington). The detection limit was 20 nmol/L bone collagen equivalents per mmol/L creatinine, with intra-assay and interassay coefficients of variation of 5.6% and 8.7%, respectively. The serum bone-formation markers, osteocalcin¹⁵ and bone-specific alkaline phosphatase, were measured with an immunoradiometric assay (Tandem-R Ostase assay; Hybritech, San Diego, California), by Dr. Gundberg of Yale University School of Medicine, New Haven, Connecticut. The detection limit for osteocalcin was 0.5 ug/L, and the intra-assay and interassay coefficients of variation were 2.3% and 8.3%, respectively. The intra-assay and interassay coefficients of variation for bone-specific alkaline phosphatase ranged from 3.7% to 6.7% and from 7.0% to 8.1%, respectively. All tests could not be run for every subject because of limited amounts of serum or urine.

Statistical Analyses

Patient characteristics and the results of laboratory tests were distributed approximately normally and were summarized with use of medians and quartiles. Analysis of variance was performed to compare the groups, with and without estrogen replacement therapy as a covariate. Unadjusted results are presented with notation when estrogen-adjusted results differed substantially. The distributions of several calcitropic hormones and biochemical values were skewed, and normality tests were rejected; therefore, medians as well as fifth and ninety-fifth percentiles are presented as summaries. The natural log transform normalized the values of 25-hydroxyvitamin D, N-telopeptides, and bone-specific alkaline phosphatase. Non-parametric tests were used for the remaining calcitropic hormones. Percentages and Fisher exact tests were used to compare groups with regard to dichotomized variables. The

TABLE II Comparison of Laboratory Tests for Osteoarthritic Women with and without Osteoporosis

Laboratory Value	Normal Range	Osteoporotic*† (N = 17)	Non-osteoporotic*† (N = 51)	P Value‡
Calcium (mg/dL)	8.8-10.5	9.6 (9.0, 11.4)	9.7 (8.6, 10.1)	0.71
Intact parathyroid hormone (pmol/L)	1.1-6.8	3.79 (1.26, 5.79)	3.26 (1.68, 6.84)	0.59
25-hydroxyvitamin D (nmol/L)	22-107§	55.0 (27.5, 82.4)	49.9 (25.0, 105.0)	0.52
1,25-dihydroxyvitamin D (pmol/L)	42-169	98.8 (18.2, 153.4)	91.0 (33.8, 143.0)	0.89
Urinary calcium (mmol/d)	1.3-10	3.28 (0.33, 5.97)	3.49 (1.50, 6.21)	0.50
Urinary N-telopeptides (nmol/L bone collagen equivalents per mmol/L creatinine)	20-76	79.0 (33.0, 133.0)	34.0 (15.0, 79.0)	0.00004
Osteocalcin (µg/L)	6-16	11.2 (0.9, 16.5)	5.2 (0.9, 14.4)	0.00020
Bone-specific alkaline phosphatase (ng/mL)	15-43	18.0 (11.0, 36.0)	16.5 (9.6, 25.0)	0.00509

*Osteoporotic subjects were those with a T score of less than -2.5, and non-osteoporotic subjects were those with a T score of at least -2.5. †The values are expressed as the median, with the fifth and ninety-fifth percentiles in parentheses. ‡The p values indicate the significance between the osteoporotic and non-osteoporotic groups after adjustment for age and estrogen intake. §Normal range designated by the manufacturer of the assay kit.

Spearman correlation coefficient was used to evaluate bivariate associations among variables. Slope comparisons were performed with the use of analysis of covariance, with the number of years since menopause, age, or the age at menopause as the covariate. P values were not adjusted for multiple statistical tests. Analyses were performed with the Statistical Analysis System (SAS Institute, Cary, North Carolina).

Results

An unexpected finding was that seventeen (25%) of the sixty-eight postmenopausal women with advanced osteoarthritis met the World Health Organization's criterion for osteoporosis (a T score for bone mineral density, at any site, of less than -2.5)¹. The subjects were stratified into osteoporotic and non-osteoporotic groups on that basis (Table I). There were significant differences between osteoporotic and non-osteoporotic subjects with regard to age ($p = 0.04$), years since menopause ($p = 0.02$), and body weight ($p = 0.0003$). By definition, the groups differed with regard to their Z scores (age-adjusted T scores). With the numbers available, the groups were not significantly different with regard to body composition, calcium intake, alcohol consumption, physical activity, or the use of estrogen-replacement therapy. The groups were significantly different with regard to smoking history ($p = 0.05$), but the number of cigarette pack-years was greater for the group of non-osteoporotic subjects than for the group of osteoporotic subjects.

Significant elevations of the markers of bone turnover were observed in subjects with low bone mineral density (Table II). Specifically, the urinary level of N-telopeptides was 2.3-fold greater, the serum level of osteocalcin was 2.2-fold greater, and the serum level of bone-specific alkaline phosphatase was 9% greater in the osteoporotic women than in the non-osteoporotic women. These biochemical markers of elevated bone turnover were inversely associated with bone density measurements at all anatomical sites (see Appendix).

Because there were significant differences in age, the age at menopause, and the number of years since menopause between the women who were osteoporotic and those who were not, comparisons of biochemical markers were retested after adjusting for those factors. The differences between the groups with regard to the levels of osteocalcin, bone-specific alkaline phosphatase, and urinary N-telopeptides remained significant ($p < 0.05$) after those analyses.

Further analyses showed that osteoporosis was indeed evident even in younger subjects. The distribution of Z scores at the trochanteric site as a function of the number of years since menopause, for example, demonstrated this point (Fig. 1). The mean Z score for the osteoporotic group was -0.55 ± 0.74 (years-since-menopause-adjusted score), -0.63 , and the mean Z score for the non-osteoporotic group was 0.96 ± 1.13 (years-since-menopause-adjusted score, 1.01) ($p < 0.0001$). Low bone density was found at all time-intervals after menopause for the osteoporotic subjects. Neither group showed a significant change in the Z score in association with

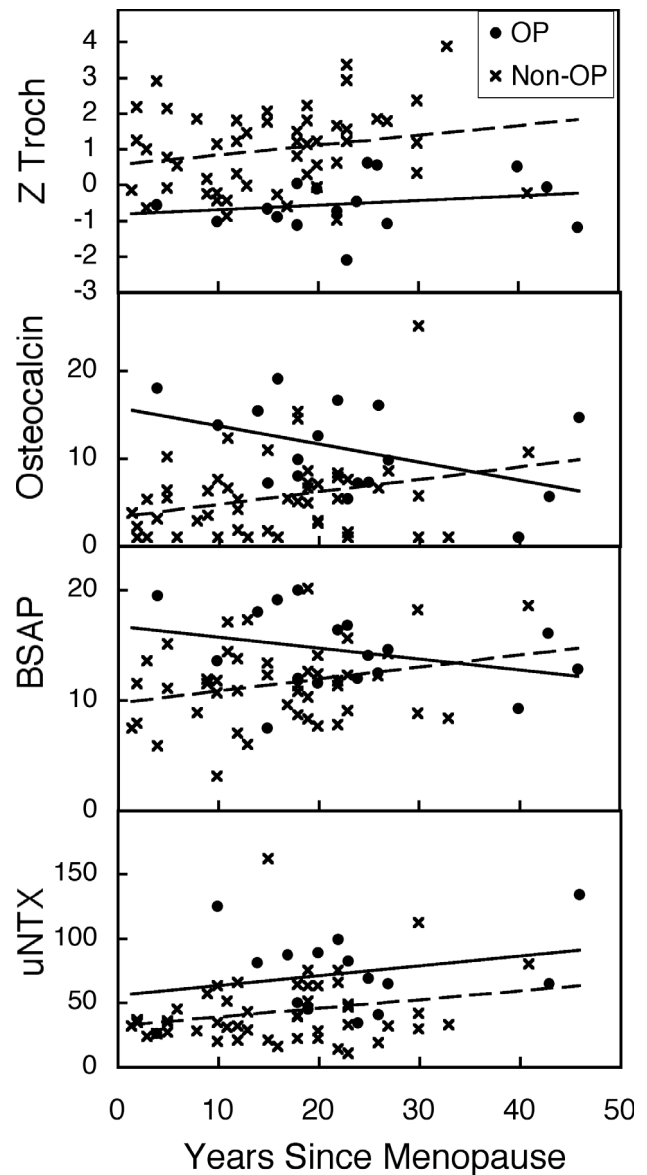


Fig. 1
Analyses of the relationships between trochanteric bone mineral density (Z-Troch), osteocalcin, bone-specific alkaline phosphatase (BSAP), and urinary N-telopeptide (uNTX) and the number of years since menopause for osteoporotic (closed circles) and non-osteoporotic (x) osteoarthritic women. Solid lines represent the correlations for osteoporotic women, and dashed lines represent the correlations for non-osteoporotic women. Between-group tests of homogeneity showed significant differences for osteocalcin ($p = 0.01$) and bone-specific alkaline phosphatase ($p = 0.04$) but not for trochanteric bone mineral density ($p = 0.60$) or urinary N-telopeptide ($p = 0.54$).

the number of years since menopause. The effect of the number of years since menopause on the Z score (that is, the slope of the regression) for the osteoporotic group (0.13 standard deviations/decade) was not significantly different from that for the non-osteoporotic group (0.27 standard deviations/de-

cade) ($p = 0.60$), with the numbers available. Osteoporosis was found even in the early postmenopausal period. Similar patterns were seen between the number of years since menopause and bone density measurements for the femoral neck, spine, and total body.

In addition, the osteoporotic group had elevated biochemical markers of high bone turnover in the early postmenopausal period (Fig. 1). There were elevated osteocalcin levels at all time-intervals in the postmenopausal period for the osteoporotic subjects. The effect of the number of years since menopause on osteocalcin was significantly different for the two groups ($p = 0.01$), with the non-osteoporotic group showing the expected increase in association with an increasing number of years since menopause. Similarly, there were elevated bone-specific alkaline phosphatase levels at all time-intervals in the postmenopausal period for the osteoporotic subjects. The effect of the number of years since menopause on bone-specific alkaline phosphatase was also significantly different for the two groups ($p = 0.04$), with the non-osteoporotic group showing the expected increase in association with an increasing number of years since menopause. There also were elevated levels of urinary N-telopeptides for the osteoporotic subjects at all time-intervals in the postmenopausal period. Although the level of urinary N-telopeptides was significantly elevated in the osteoporotic group after adjustment for the number of years since menopause ($p = 0.0004$) and was elevated in the osteoporotic group in the early menopausal period, the osteoporotic and non-osteoporotic groups showed a similar ($p = 0.54$) but slight effect of the number of years since menopause on urinary N-telopeptides. Thus, advanced age or a greater number of years since menopause did not explain the osteoporosis seen in these osteoarthritic women. These analyses ruled out the possibility that the osteoarthritic women with osteoporosis were simply older than those without osteoporosis.

There were no significant differences between the two study groups with regard to the median values for serum calcium, 25-hydroxyvitamin D, and parathyroid hormone with the numbers available, but not all values were within the normal range (Table II). Evaluation of these calcitropic hormones revealed that fifteen (22%) of these sixty-eight osteoarthritic women were vitamin-D deficient (currently defined as a 25-hydroxyvitamin-D level of <37.5 nmol/L¹³) and three had elevations of parathyroid hormone (>6.8 pmol/L). Of the seventeen osteoporotic women, only two had vitamin-D deficiency and none had hyperparathyroidism. Of the fifty-one non-osteoporotic women, thirteen (25%) had vitamin-D deficiency and three (6%) had hyperparathyroidism. With the numbers available, the percentages of subjects with vitamin-D deficiency ($p = 0.32$) and hyperparathyroidism ($p = 0.57$) were similar for both groups. A more stringent threshold for vitamin-D deficiency (<30 nmol/L¹⁶) showed that one (6%) of the seventeen osteoporotic women and six (12%) of the fifty-one non-osteoporotic women had vitamin-D deficiency, but this difference between the groups was still not significant ($p = 0.67$) with the numbers available.

Discussion

In the present study, 25% (seventeen) of sixty-eight postmenopausal white women with advanced osteoarthritis requiring total hip arthroplasty had occult osteoporosis, defined as a bone-mineral-density T score of less than -2.5 . Several studies have examined the relationship between osteoarthritis and bone density, either at the affected joint or at distant sites. With use of the Singh index as a measure of trabecular bone mass, Cooper et al. reported higher values for femoral heads that had radiographic evidence of osteoarthritis¹⁷. Several investigators have reported elevated bone mineral density in subjects with osteoarthritis¹⁸⁻²⁰ but, in a detailed study of monozygotic and dizygotic twins, increased bone mineral density in osteoarthritic subjects was found only at the affected site and not at other sites²¹. Although osteoarthritis may confound densitometry at the affected joint, the artifact is usually toward elevated bone mineral density because of osteophytes or focal osteosclerosis. In the present study, bone mineral density was measured at multiple sites and all seventeen subjects who were classified as osteoporotic (on the basis of the bone mineral density at any site being greater than 2.5 standard deviations below the mean value for young normal individuals¹) had, in fact, low bone mineral density at each measurable site. Bone density measurements indicate the net skeletal mass, and biochemical markers of bone turnover can be valuable because they reveal continued loss of bone and the need for systemic treatment.

The results of this study pertain to postmenopausal white women only. This study is limited because the subjects were not enrolled in a case-matched manner or with the intent to examine racial or ethnic effects. There were significant differences between the osteoporotic and non-osteoporotic groups with regard to age and the number of years since menopause. This raised the concern that the women with low bone density and elevated bone markers were simply older than those in the normal group. Detailed analysis, however, showed that age, the number of years since menopause, physical activity, calcium intake, estrogen use, alcohol intake, and percentage of body fat did not account for the low bone density and elevated biochemical markers of high bone turnover.

Our findings clearly reject the hypotheses that all osteoarthritic women are protected against bone loss and that they are protected during the early postmenopausal period. The biochemical evidence of high bone turnover in these women and its occurrence in the early postmenopausal period appear to indicate that the diagnosis of osteoarthritis does not eliminate the risk of accelerated bone loss or the need to evaluate bone mineral density in all postmenopausal women with osteoarthritis.

Because both diseases demonstrate a family history, it is likely that genetic factors that may be associated with the acquisition of peak bone mass or with the rate of bone loss may, in part, account for the elevated bone mineral density that has been reported for some younger women with osteoarthritis^{22,23}. Another large study showed that osteoarthritic women


had low rates of bone loss at the femoral neck²⁴.

We evaluated these subjects with regard to other factors that could explain the low bone density. Validated questionnaires showed little differences in the current extent of physical activity, calcium intake, alcohol consumption, or estrogen use. Lifestyle factors may be of limited value in a study such as this one because they do not describe the past behavior of the subjects. The duration of estrogen use, the history of exercise, calcium intake (especially in the teenage years), and other factors could contribute to bone density at the time of enrollment.

The prevalence of vitamin-D deficiency was not greater in the osteoarthritic women with low bone density than it was in those without osteoporosis. Thus, factors other than vitamin-D deficiency must have contributed to the low bone mass. Nevertheless, the detection of vitamin-D deficiency in 22% (fifteen) of these osteoarthritic women raises concerns about their nutritional status when they presented for total hip arthroplasty. Hypovitaminosis D is a public-health problem that is of concern among the elderly and hospitalized populations²⁵. We previously reported that 50% (fifteen) of thirty postmenopausal, community-living women who presented with a hip fracture and had no secondary cause of osteoporosis had deficient levels of 25-hydroxyvitamin D (using the more stringent definition of <30 nmol/L)⁹. Bone biopsies were not done in that study or in the present study, thus precluding information about osteomalacia; however, vitamin-D deficiency has been associated with osteomalacia and the occurrence of fractures^{26,27} and bone pain²⁸. Avoidance and correction of vitamin-D deficiency is an inexpensive task and may require the education

of clinicians and important changes in the practice of care for subjects admitted to orthopaedic services²⁹. The current recommended daily intake of vitamin D supplements is 400 to 800 IU, with the higher dose for women over the age of seventy years³⁰.

Appendix

 A table showing correlations between bone density at specific sites and biomechanical markers of bone turnover is available with the electronic versions of this article, on our web site at www.jbjs.org (go to the article citation and click on "Supplementary Material") and on our quarterly CD-ROM (call our subscription department, at 781-449-9780, to order the CD-ROM). ■

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