Alexandria Journal of Medicine (2011) **47**, 149–155

Alexandria University Faculty of Medicine

Alexandria Journal of Medicine

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ORIGINAL ARTICLE

The relationship between osteoarthritis of the hands, bone mineral density, and bone turnover markers

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Received 27 May 2011; accepted 23 June 2011
Available online 9 August 2011

KEYWORDS

Hand osteoarthritis;
Bone mineral density;
Bone turnover markers;
Osteoporosis

Abstract *Aim:* To investigate the relationship between hand osteoarthritis (HOA), bone mineral density (BMD), and bone turnover markers.
Methods: Twenty post-menopausal women aged 50–73 years (mean: 62.4 ± 6.5) diagnosed with HOA were recruited along with 10 age-matched post-menopausal women with no signs of HOA as the control group. Both groups had postero-anterior hand radiographs taken and evaluated according to the Kellgren–Lawrence scale to assess OA severity. They underwent thorough clinical examination including measurement of body mass index (BMI). They completed the AUSCAN

Abbreviations: HOA, hand osteoarthritis; BMD, bone mineral density; BMI, body mass index.

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Peer review under responsibility of Alexandria University Faculty of Medicine.
doi:10.1016/j.ajme.2011.06.009

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questionnaire. Grip strength was measured using a hand held dynamometer and lateral pinch strength was measured using a pinchmeter. They underwent BMD measurement at the hip and wrist using Dual energy X-ray absorptiometry. Furthermore, they had serum osteocalcin and urinary deoxypyridinoline (DPD) measured.

Results: There was no statistically significant difference in *T*-scores of the hip ($P = 0.168$) and wrist ($P = 0.45$) between the patients and the controls. However, six patients (30%) had osteoporosis. A total of 12 patients had diminished BMD at the hip. There was no significant increase in serum osteocalcin levels in patients compared to controls ($P = 0.382$). However, urinary DPD was significantly elevated in the patient group compared to the controls, ($P < 0.0001$). There was a positive correlation between *T*-scores at the hip and BMI ($P = 0.017$). There was a negative correlation of *T*-scores at the hip and wrist with postmenopausal duration and parity. There was no correlation between the *T*-scores and bone turnover markers. There was a positive correlation between OA severity and both *T* and *Z*-scores at the wrist.

Conclusions: Although there was no significant association between HOA and BMD, HOA is associated with increased bone turnover as demonstrated by the significant elevation in urinary DPD. These patients should be followed up to assess the need for medical treatment to prevent future fractures.

1. Introduction

Osteoarthritis (OA) is the most frequent rheumatic joint disease.[1] The prevalence of OA increases with age with evident sex-specific differences.[2] Before the age of 50, the prevalence of OA in most joints is greater in males than in females. However, hand OA (HOA) is more prevalent among women.[2,3] In the past, research in OA was directed towards the knee and hip. Information and research results on HOA are relatively limited although it can have a significant impact on function and activities of daily living causing disability and lifestyle changes.[4]

Osteoporosis (OP) is also a prevalent condition that is estimated to affect 1 out of 5 women by the age of 80. Thus OP and OA are both common conditions that are more likely to affect females more than males. However, it's rather unusual to find both conditions in the same individual.[5]

Several studies have revealed increased bone mineral density (BMD) in patients with knee or hip OA. One hypothesis suggests that the local increase in BMD in osteoarthritic joints may be due to decreased shock absorption in them.[6] On the other hand, it has been proposed that thickening and stiffening of the subchondral bone with increased BMD may lead to the development of OA.[7] However, a limited number of studies have addressed the issue of BMD changes in HOA. The results of these studies have been inconsistent compared with controls with some authors citing an association with OP, while others noting an increase in BMD.[8–14]

Most authors have assessed BMD by Dual energy X-ray absorptiometry (DEXA) and ultrasound (US) attenuation.[8–14] Few have measured bone turnover markers as osteocalcin, which is a marker of bone formation or urinary deoxypyridinoline (DPD), which is a marker of bone resorption. This study aimed at investigating the relationship between HOA, BMD and bone turnover markers.

2. Methods

Twenty post-menopausal females aged 50–73 (mean: 62.4 years) diagnosed with HOA according to the ACR criteria were enrolled in this study.[15] Patients with other known arthropathies, secondary OA or causes of secondary osteoporosis were excluded. Ten age-matched females with no signs of hand OA served as the control group.

Full demographic data was obtained, including information on medications and any medical disorders. Body mass index (BMI) was calculated (kg/m^2) and all patients and controls underwent thorough clinical examination and completed the Australian/Canadian OA hand index (AUSCAN) which is a disease-specific health status measure for HOA.[16] It assesses pain (five items), stiffness (one item), and function (nine items). The Likert-scale version (0–4) was used in this study for the 15 items.

Grip strength was measured in kilograms bilaterally using a hand held dynamometer. The patients were tested while they were comfortably seated with the elbow flexed to 90° and the wrist positioned between 0° and 30° of extension. Lateral pinch strength was also measured in kilograms bilaterally using a pinchmeter.[17] In both cases the best performance out of three trials was recorded.

Postero-anterior hand radiographs were taken and evaluated according to the Kellgren–Lawrence (K–L) scale.[18] The criteria for increasing severity of OA relate to the sequential appearance of osteophytes, joint space loss, subchondral sclerosis, and cyst formation. (0: no OA, 1: doubtful, 2: minimal, 3: moderate, and 4: severe). Definite HOA is diagnosed with a grade of $\geqslant 2$.

2.1. Bone mineral density measurements

All participants underwent BMD measurements at the hip (femoral neck) and the wrist (anterior–posterior view) by the same DEXA equipment (Discovery QDR series W).[19,20] In agreement with the WHO criteria, osteopenia (low bone mass) was defined as a *T*-score between -1 and -2.5 and OP as a *T*-score $\leqslant -2.5$.

2.2. Laboratory testing

The patients underwent the following lab investigations:

1. Routine chemistry tests including serum calcium, phosphorus, and alkaline phosphatase were measured using Dimension RXL max autoanalyzer from Dade Behring (Siemens). This was done to rule out secondary causes of OP.
2. *Serum osteocalcin:* which is a marker of bone formation and turnover reflecting increased osteoblastic activity (new bone synthesis) was measured by the aid of IMMULITE 2000 analyzer.
3. *Urinary DPD:* is a marker of bone resorption, reflecting the activity of osteoclasts and collagen degradation. It is excreted un-metabolized in urine and is unaffected by diet, making it suitable for assessing resorption. It was also measured using competitive immunoassay using the IMMULITE 2000 analyzer.

2.2.1. Technical points

All samples were collected in the early morning before 10 am to avoid diurnal variations. Blood was collected using vein puncture with hemolysis avoidance; the samples were immediately separated and kept frozen until assayed.

2.3. Statistics

Statistical analysis was carried out using the statistical package of social science (SPSS version 18). Descriptive data was expressed as mean and standard deviation. Univariate analyses including *t*-test and Mann–Whitney test were used to test the significance of the results of quantitative variables. Moreover, Fisher's exact test was used to test for significance among qualitative variables. Linear correlations were conducted to show the relationship between *T*-scores of the hip and wrist, OA severity and other studied parameters. The significance of the results was at the 5% level of significance.

3. Results

Table 1 shows the demographic data of the patients and controls, including age, BMI, parity, and post-menopausal duration. There was no statistically significant difference between the two groups.

According to the K–L grading system, 11 patients (55%) had grade 2 HOA, whereas eight (40%) had grade 3 and only one patient (5%) had grade 4 HOA. Four patients had evidence of erosions (Fig. 1).

Table 1 Demographic data of the patients and controls.

Variable	Controls (n = 10)	Patients (n = 20)	t-Test (P)
Age			
Range	50–76	50–73	
Mean ± SD	58.1 ± 6.8	62.4 ± 6.5	P = 0.103
BMI			
Range	28.4–45.7	28–42.8	
Mean ± SD	36.6 ± 5.2	34.5 ± 4.3	P = 0.254
Parity			
Range	0–8	0–9	
Mean ± SD	4.0 ± 2.4	4.2 ± 2.4	P = 0.88
Postmenopausal duration (years)			
Range	1–25	3–25	
Mean ± SD	10.1 ± 8.0	15.4 ± 7.1	P = 0.075

n = Number.
Fisher's exact test.

Table 2 shows the results of DEXA for the patients and controls as well as the levels of bone turnover markers. Regarding the patients, the mean *T*-score of the hip was −1.2 ± 0.9, and −1.4 ± 1.4 in the wrist. There was no statistically significant difference in *T*-scores of the hip and wrist between the patients and the controls (P = 0.168 and 0.45, respectively), and no statistically significant difference in *Z*-scores of the hip (P = 0.713) and wrist (P = 0.601). Six patients (30%) had OP (one in the hip and five in the wrist shown in Figs. 2 and 3). Out of all the studied patients, 16 had evidence of diminished BMD; five in the hip, four in the wrist, and seven had both hip and wrist involvement. Only one control had evidence of OP at the wrist.

Serum calcium (mean: 9.04 ± 0.4), phosphorus (mean: 3.79 ± 0.28) and alkaline phosphatase levels (mean: 101.7 ± 16.3) were within normal limits in the studied patients. Three patients had elevated serum osteocalcin (mean: 37.3 ± 10.2), whereas 17 patients had elevated urinary DPD (mean: 8.62 ± 2.6). There was no statistically significant difference between the patients and controls regarding osteocalcin levels. However, there was a statistically significant difference between the two groups in urinary DPD levels (P < 0.0001).

When the HOA patients with OP were compared to patients within the same group without OP, there was no statistically significant difference between them regarding age and BMI (Table 3). However, the patients who had OP had significantly higher parity compared to the patients who did not have osteoporosis (P = 0.041).There was no statistically significant difference between the patients with OP and those without OP regarding serum osteocalcin and urinary DPD levels (P = 0.631 in each).

Table 4 shows the correlation between BMD (*T*-score of the hip and wrist) and the different studied parameters. BMI was positively correlated with *T*-scores of the hip (r = 0.528, P = 0.017) but not with that of the wrist. Parity was negatively

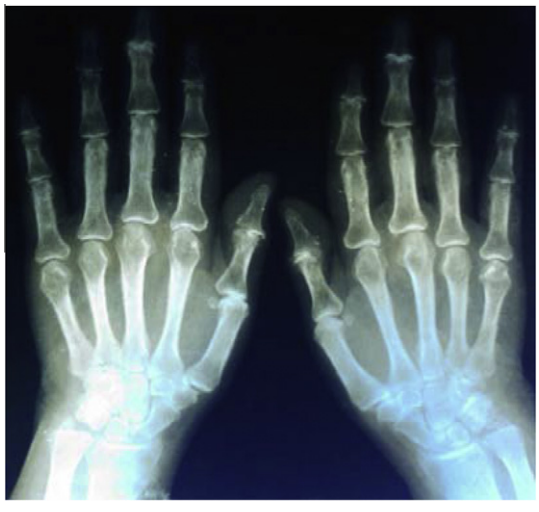

Figure 1 Posteroanterior radiograph of the hands in a patient revealing narrowing and osteophytes affecting multiple interphalangeal joints. Note the "gull-wing" configuration of the distal interphalangeal joint of the middle finger due to central erosion.

Table 2 Results of bone mineral density (BMD) measured by DEXA and bone turnover marker levels in patients and controls.

BMD	Controls ($n = 10$)	Patients ($n = 20$)	t-Test (P)
T-score hip			
Range	−2.4–1.4	−2.7–1.0	
Mean ± SD	−0.65 ± 1.04	−1.2 ± 0.9	$P = 0.168$
T-score wrist			
Range	−2.9–1.2	−4.6–0.6	
Mean ± SD	−0.98 ± 1.2	−1.4 ± 1.4	$P = 0.45$
Z-score hip			
Range	−1.2–2.0	−4.6–2.1	
Mean ± SD	0.19 ± 0.91	0.002 ± 1.4	$P = 0.713$
Z-score wrist			
Range	−1.2–1.9	−2.0–2.6	
Mean ± SD	0.006 ± 1.02	0.3 ± 1.2	$P = 0.601$
Osteocalcin			
Range	7.8–57.0	32.0–45.0	
Mean ± SD	37.3 ± 10.2	40.3 ± 4.2	$P = 0.382$
DPD			
Range	1.21–12.5	3.9–5.1	
Mean ± SD	8.62 ± 2.6	4.6 ± 0.4	$P < 0.0001$*

* Significant at $P \leqslant 0.05$.

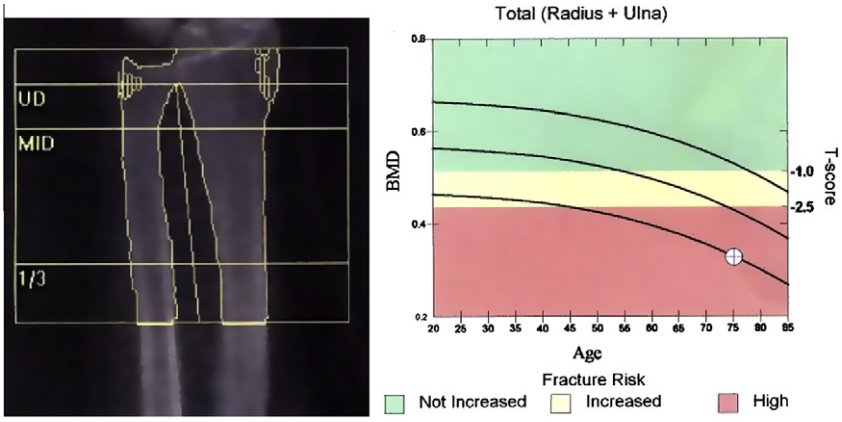

Figure 2 DEXA scan over the wrist in a patient revealing decreased BMD in the osteoporotic range with high risk of fracture.

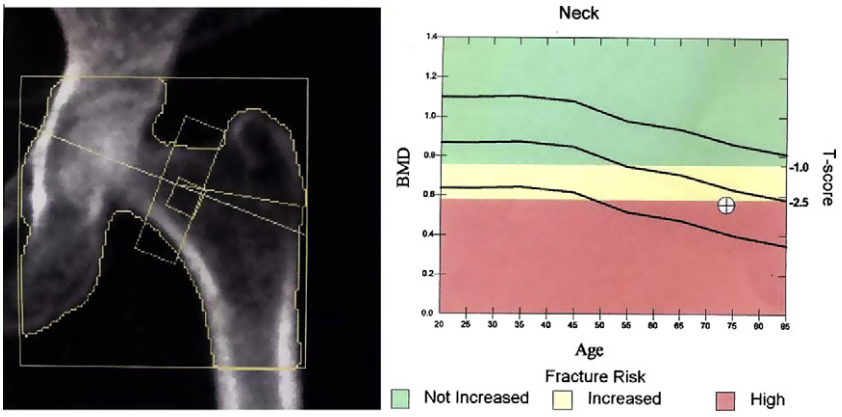

Figure 3 DEXA scan over the femoral neck in a patient revealing decreased BMD in the osteoporotic range.

correlated with T-scores of the wrist ($r = -0.522$, $P = 0.026$). There was a negative correlation between the duration of menopause and T-scores in the hip and wrist ($P = 0.001$ and 0.009, respectively). There was no correlation between T-scores at the

Table 3 Comparison between hand osteoarthritis (HOA) patients with and without osteoporosis (OP).

	HOA with OP (n = 6)	HOA without OP (n = 14)	Mann–Whitney test
Age			
Range	50–70	53–73	$Z = -0.619$
Mean ± SD	65.5 ± 7.84	61.0 ± 5.57	$P = 0.109$
Body mass index			
Range	28–39.7	28.4–42.8	$Z = 0.149$
Mean ± SD	32.23 ± 4.32	35.46 ± 4.04	$P = 0.153$
Parity			
Range	3–9	0–7	$Z = -0.07$
Mean ± SD	5.83 ± 2.48	4.0 ± 1.59	$P = 0.041$*
Osteocalcin			
Range	28.9–49	7.8–57	$Z = -0.494$
Mean ± SD	37.75 ± 7.55	37.12 ± 11.39	$P = 0.631$
DPD			
Range	1.21–10.5	4.8–12.5	$Z = -0.493$
Mean ± SD	7.57 ± 3.36	9.07 ± 2.19	$P = 0.631$

Z, Mann–Whitney test; P, Fisher's exact test.
* Significant at $P \leqslant 0.05$.

Table 4 Correlations between T-scores of the hip and wrist and other studied parameters in the patients.

Studied parameters	T-score hip		T-score wrist	
	r	P	r	P
Age	−0.296	0.204	−0.277	0.237
BMI	0.528	0.017*	0.19	0.423
Parity	−0.369	0.131	−0.522	0.026*
Postmenopausal duration	−0.568	0.001*	−0.469	0.009*
Osteocalcin	0.128	0.591	0.058	0.807
DPD	0.41	0.071	0.211	0.372
Erosions	−0.065	0.785	0.043	0.856
Right grip	0.309	0.185	0.43	0.058
Left grip	0.312	0.143	0.348	0.133
Right pinch	0.25	0.288	0.15	0.527
Left pinch	0.331	0.154	0.296	0.205
Auscan	−0.022	0.927	−0.276	0.239
Pain	0.051	0.829	−0.216	0.361
Stiffness	0.147	0.537	−0.143	0.548
Function	−0.07	0.769	−0.289	0.216

* Significant at $P \leqslant 0.05$.

Table 5 Correlation between hand osteoarthritis (HOA) severity and the different parameters measured in the patients.

	Correlation with HOA severity	
	r	P
Age	0.102	0.67
BMI	0.288	0.218
T-score hip	0.175	0.461
T-score wrist	0.506	0.023*
Z-score hip	0.232	0.325
Z-score wrist	0.515	0.02*
Erosions	0.259	0.27
Osteocalcin	−0.124	0.366
DPD	0.073	0.76
Right grip	0.189	0.424
Left grip	0.163	0.49
Right pinch	0.027	0.911
Left pinch	0.148	0.534
Auscan	−0.133	0.577
Pain	0.095	0.692
Stiffness	0.067	0.778
Function	−0.258	0.272

* Significant at $P \leqslant 0.05$.

hip or wrist and age, hand function, erosions, and bone turnover markers (osteocalcin and DPD).

Table 5 shows the correlation between HOA severity assessed by K–L grading and the different parameters measured among the studied patients. There was a positive correlation between OA severity and the T and Z-scores of the wrist (P = 0.023 and 0.02, respectively). However, OA severity did not correlate with age, BMI, bone turnover markers, grip/pinch strength, and AUSCAN score (hand pain, stiffness, and function).

4. Discussion

Several studies have revealed increased BMD in patients with knee or hip OA. However, this association is less obvious in subjects with HOA.[21] In the current study, six patients had evidence of OP; one in the hip and five in the wrist. Out of all the studied patients, 16 had evidence of diminished BMD; five in the hip, four in the wrist, and seven had both hip and wrist involvement. However, there was no statistically significant difference between the patients and controls regarding BMD measured by DEXA. Sowers et al.[14] found no difference in the mean BMD levels when comparing women with prevalent HOA with women without HOA. Belmonte-Serrano et al.[8] and Schneider et al.[12] found a negative association between HOA and BMD at axial sites. However, Marcelli et al.[13] and Haugen et al.[21] found BMD to be increased in patients with HOA compared to controls. On the other hand, two longitudinal studies did not find any associations between HOA and bone mass at appendicular sites.[10,11]

These contradicting results in axial BMD measurements may partly be due to radiographic versus clinical definition of HOA,

where hand radiographs tend to over-diagnose OA.[12] In most studies, HOA is defined radiographically according to the Kellgren–Lawrence scale.[18] Another study in which HOA was diagnosed according to the ACR clinical classification criteria demonstrated significantly lower BMD levels in HOA compared to controls.[13] In the current study, HOA was diagnosed according to the ACR criteria and confirmed by hand radiographs.

Other factors that may contribute to the conflicting results are erosive versus non-erosive HOA, multi-joint versus isolated HOA, hormonal influences, misdiagnosis of HOA,[13,22] as well as the method of BMD assessment. El-Sherif et al.[23] reported low BMD in HOA using phalangeal BMD. Haara et al.[24] found a direct relation between HOA and low cortical bone mineral mass using calcaneal broad band US attenuation and by measuring combined cortical thickness and metacarpal index. He cited that symmetrical distal interphalangeal OA in hand joints significantly predicted low values of calcaneal broad band US attenuation after following up his patients 20 years later. He noted an increased risk of OP over time.

Previous studies have shown that local biomechanical changes are responsible for BMD changes in the hand. However, they cannot account for BMD changes at sites remote from the osteoarthritic process. It has been suggested that genetic and metabolic factors may explain the direct relation of HOA with low cortical bone mineral mass.[24]

Haugen et al.[21] demonstrated elevated BMD at axial sites and attributed this to systemic intrinsic variations in bone structure, quality, and metabolism rather than a consequence of local mechanical conditions.[25–28] He measured BMD at the hip and lumbar spine. However, the presence of osteophytes in patients with lumbar osteoarthritis may contribute to the overestimation of lumbar spine BMD measurements.[29] This is the reason why we did not perform DEXA on the lumbar spine.

In longitudinal studies, prior to joint space narrowing, cortical plate thickness in the wrist and hand increased in 2/3 of patients and decreased in 1/3. The decrease was attributed to localized periarticular inflammation,[29] whereas the increase was due to osteophyte formation.[30]

BMI was positively correlated with *T*-score of the hip ($P = 0.017$) but not with that of the wrist. This can be explained by the fact that the hip is a weight-bearing joint whereas the wrist is not. In fact it would be expected that the BMD measured at the wrist to be relatively low in HOA due to limited use caused by the pain experienced in the hand joints. Hochberg et al. found that women with radiographic HOA had a significantly greater adjusted rate of bone loss at the radius than women with normal hand radiographs.[31]

When the patient group was subdivided into those with OP and those with no OP, the OP group had significantly higher parity. This confirms the effect of parity on BMD. Parity and postmenopausal duration were negatively correlated with BMD. These are known risk factors for OP.[32,33] BMD measured at the wrist was positively correlated with the severity of HOA. This is in agreement with Haugen et al.[21] This positive association may be explained by the presence of osteophytes which is more prominent in severe cases of HOA.

In this study, only three patients (15%) had elevated serum osteocalcin levels. There was no statistically significant difference between patients and controls. Sowers noted that average osteocalcin levels were 25–35% lower in women with HOA compared to women without HOA and this finding persisted after adjusting for age, BMI, smoking, and menstrual status.[5]

Dequeker et al.[34] found more bone and higher levels of osteocalcin among women with HOA and concluded that this represented a stiffer bone. Sharif et al.[35] associated higher serum osteocalcin levels with late-phase bone scan abnormalities. Campion et al.[36] suggested that higher levels of serum osteocalcin were found primarily in a small number of patients with destructive OA, and lower levels of serum osteocalcin were observed in patients with non-destructive OA. Sowers et al.[5] suggested that bone turnover would be expected to increase if the OA process becomes increasingly destructive. In this study, four patients had evidence of erosive HOA; however, erosions did not correlate with BMD measured by DEXA or bone turnover markers.

Seventeen patients (85%) had increased urinary DPD levels. There was a statistically significant difference between patients and controls. This is an indicator of active bone turnover. However, there have not been any studies to date in the literature measuring urinary DPD levels in HOA.

Diagnosis of OP is not based on the evaluation of bone markers, and BMD assessment is still the standard criterion for evaluation and diagnosis. However, mean values for markers of bone turnover are higher in OP patients than in matched controls. In various studies, the mean urinary excretion of DPD is 20–100% higher in patients with OP than in healthy subjects. BMD is an important predictor of fracture risk; however, a single measurement indicates only current BMD, not the anticipated rate of bone loss.[37] However, bone turnover markers do predict, with some degree of confidence, the degree of bone loss. They are useful to categorize an individual as having fast or slow bone turnover.[38]

Bone biomarkers provide an assessment of the dynamic aspects of skeletal metabolism as opposed to the more static assessment by DEXA. In other words, DEXA measures BMD without specifying when the changes occurred, whereas bone turnover markers represent ongoing changes in BMD.

Clinical symptoms and functional disability were not correlated with OA severity assessed by radiographic findings. This is consistent with Poiraudeau.[39] Baron et al.[40] suggested that this was related to the neuromuscular condition rather than articular degeneration. There was no correlation between BMD and hand function. This supports the fact that diminished BMD is not solely associated with disuse but can probably be due to genetic causes as well.

5. Conclusion

Although there was no significant association between HOA and BMD, HOA is clearly associated with increased bone turnover as demonstrated by the significant elevation in urinary DPD. These patients should be followed up to assess the need for medical treatment to prevent future fractures.

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