Bone Mass, Bone Microstructure and Biomechanics in Patients with Hand Osteoarthritis

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ABSTRACT
The impact of primary hand osteoarthritis (HOA) on bone mass, microstructure, and biomechanics in the affected skeletal regions is largely unknown. HOA patients and healthy controls (HCs) underwent high-resolution peripheral quantitative computed tomography (HR-pQCT). We measured total, trabecular, and cortical volumetric bone mineral densities (vBMDs), microstructural attributes, and performed micro–finite element analysis for bone strength. Failure load and scaled multivariate outcome matrices from distal radius and second metacarpal (MCP2) head measurements were analyzed using multiple linear regression adjusting for age, sex, and functional status and reported as adjusted Z-score differences for total and direct effects. A total of 105 subjects were included (76 HC: 46 women, 30 men; 29 HOA: 23 women, six men). After adjustment, HOA was associated with significant changes in the multivariate outcome matrix from the MCP2 head (p < .001) explained by an increase in cortical vBMD (ΔZ = 1.07, p = .02) and reduction in the trabecular vBMD (ΔZ = −0.07, p = .09). Distal radius analysis did not show an overall effect of HOA; however, there was a gender-study group interaction (p = .044) explained by reduced trabecular vBMD in males (ΔZ = −1.23, p = .02). HOA was associated with lower failure load (−514 N; 95%CI, −1018 to −9; p = 0.05) apparent in males after adjustment for functional status. HOA is associated with reduced trabecular and increased cortical vBMD in the MCP2 head and a reduction in radial trabecular vBMD and bone strength in males. Further investigations of gender-specific changes of bone architecture in HOA are warranted. © 2020 The Authors. Journal of Bone and Mineral Research published by American Society for Bone and Mineral Research.

KEY WORDS: OSTEOARTHRITIS; DISEASES AND DISORDERS OF/RELATED TO BONE; BONE QCT/MICROCT; ANALYSIS/QUANTITATION OF BONE; BIOMECHANICS; ORTHOPAEDICS

Introduction
Osteoarthritis of the hand (HOA) is a highly prevalent rheumatic disorder, the burden of which increases with age. Clinical manifestation of HOA can vary, ranging from a mild disease, characterized by Heberden’s node formation at the distal interphalangeal joints, to a severe disease with decline in function, especially if proximal hand joints become involved. The clinical burden of HOA comprises pain and joint deformity, which can lead to loss of grip strength and impairment in hand function subsequently influencing patients’ quality of life. Despite increasing efforts to homogenize diagnostic criteria, define therapeutic and research targets, and formulate imaging recommendations for HOA, no breakthrough has been made toward an effective treatment, often limiting HOA management to symptomatic treatment with nonsteroidal anti-inflammatory drugs (NSAIDs). Recently, studies using biologic agents or hydroxychloroquine also failed to show effects on symptoms, magnetic resonance imaging (MRI)-based inflammation, or NSAID intake.

HOA is defined by its clinical appearance by the 1990 American College of Rheumatology (ACR) classification criteria. On the other hand, several imaging studies using MRI and ultrasound have shown that HOA can exhibit signs of inflammation such as synovitis and osteitis, which are considered predictors for disease progression. Functional decline in the course of HOA together with inflammatory changes could progressively alter the bone architecture of the affected anatomical sites in HOA. Few is known about this aspect of the disease, although clinical observations suggest that the articular bone surface is altered in some HOA patients, as evidenced by the formation of bone erosions in a subset of the patients.

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To exactly define the impact of HOA on the bone, we decided to apply high-resolution peripheral quantitative computed tomography (HR-pQCT), which allows us to separately quantify cortical and trabecular bone mass, analyze the bone microarchitecture, and calculate the biomechanical properties of the bone using micro–finite element analysis (μFEA). During the recent years, HR-pQCT has been progressively used to characterize bone in various forms of inflammatory arthritis, although no data on bone structural and functional properties are yet available from HOA patients. Hence, in order to define the impact of HOA on bone we performed a study comparing healthy individuals with HOA patients and analyzed bone mass, microstructure and function in the skeletal regions, which are functionally affected by the disease. To accomplish this, HR-pQCT analyses of the radius and the fingers were done in HOA patients and respective healthy controls (HCs).

**Patients and Methods**

Osteoarthritis patients and controls

Patients with HOA and HCs were part of the Erlangen Imaging Cohort (ERIC), which prospectively assesses bone composition in healthy individuals and patients with arthritis. All consecutive HOA patients were recruited at the Department of Internal Medicine 3 of the University of Erlangen-Nuremberg (SU) and were clinically examined by an experienced rheumatologist (AK, SB, JR, AH). All HOA patients fulfilled the 1990 ACR criteria for the classification of HOA. HOA patients were excluded if they had concomitant inflammatory diseases such as rheumatoid arthritis, psoriatic arthritis, or chronic inflammatory bowel disease. Furthermore, they had to be negative for rheumatoid factor (RF) or anti-cyclic citrullinated protein antibodies (ACPA), and they were not allowed to have a history of psoriasis.

HCs were recruited through a field campaign. Only subjects who were free of present or past signs of rheumatic disease were included. Clinical assessment (AK, SB, JR, AH) was performed to rule out tenderness, swelling, and bony swelling. HCs with a history of osteoporosis, pathological fractures, recent trauma (<1 year) or those having received glucocorticoids or bisphosphonates were excluded. Diabetes mellitus, gastrointestinal, cardiovascular (angina, myocardial infarction, stroke), renal disease, or hepatic disease also led to exclusion. All HCs had to be RF-negative and ACPA-negative.

In all participants smoking status, alcohol intake, body mass index (BMI, kg/m²), and physical function by health assessment questionnaire (HAQ-DI) were recorded. Clinical parameters of HOA patients such as presence of hand pain, tender and swollen joints, bony swellings, stiffness, the duration of stiffness, the score for assessment and quantification of chronic rheumatic affections of the hands (SF-SACRAH) and the intake of NSAIDs in the last 3 months, was also collected. All subjects gave informed consent. The ethical committee of the University Clinic of Erlangen (276, 14 B) and the National Radiation Safety Agency (ZS-22462/2) approved the study.

Acquisition of HR-pQCT data

HR-pQCT of the 2nd and 3rd metacarpophalangeal (MCP) joints, and the distal radius of the same extremity was performed using the XtremeCT I scanner (Scanco Medical, Brütisellen (openVMS; V6.0), Switzerland). The dominant hand was scanned in each subject. Measurements of the MCP joints were performed as described using 322 slices and the whole 2nd metacarpal (MCP2) head was segmented as described. The distal radius was measured using the manufacturer’s default protocol for in vivo patient imaging. Measurements were carried out with an offset of 9.5 mm proximal to the reference line, which was manually set, and the usage of 110 slices. Before the assessment of structural changes and the evaluation of μFEA, each image was scored for motion artifacts. Only images with a motion grade 1 to 3 were evaluated.

Assessment of bone density and bone microstructure

Standard analysis software (V.6.0) was used to determine the following density measurements of the distal radius and the MCP2 head: volumetric bone mineral density (vBMD) of total (total vBMD), trabecular (Tb.vBMD), and cortical bone (Ct.vBMD). For the distal radius, also meta-trabecular (MetaTrab.vBMD), inner-trabecular (InnerTrab.vBMD) (all mg hydroxyapatite [HA]/cm³), ratio of meta-to-inner density (Meta/Inn, %), and cross-sectional bone area (mm²) were assessed. At the distal radius the bone microstructure was evaluated by determining trabecular bone volume fraction (BV/TV, %), trabecular number (Tb.N, 1/mm), thickness (Tb.Th, mm), separation (Tb.Sp, mm), network inhomogeneity (SD of 1/trabecular number [Tb.1/N.SD], mm), as well as cortical thickness (Ct.Th, mm).

μFEA

μFEA on radial bone was performed with the FAIM software (V.8.0; Numerics88 Solution, Calgary, Canada) using the segmented trabecular network and cortex of the HR-pQCT images. Mesh size of the resulting models ranged from 1.5 to 3.5 million equally sized brick elements. Single linear isotropic tissue modeling was applied by assigning a tissue modulus of 6829 MPa and a Poisson ratio of 0.3 homogeneously to each element. A linear uniaxial compression test was simulated. Nodes on the proximal bone surface were fixed in the z direction but unconstrained in the x and y directions. Nodes on the distal bone surface were also free in the x and y direction but exposed to a displacement equivalent to 1% strain along the z axis. We estimated failure load (N) based on the Pistoia criterion; namely axial bone stiffness (kN/mm) as reaction force (RFx) divided by average displacement of the distal surface (Uz) and bone strength.

Assessment of erosions and osteophytes

Two independent and blinded readers assessed the total number of osteophytes and erosions of the MCP joints 2 and 3 (DS, AB). Erosions were defined as juxta-articular breaks of the cortical shell, detectable in two consecutive slices and in two vertical planes. An osteophyte was defined as a bony outgrowth occurring adjacent to the joint. Erosions and osteophytes were assessed to investigate their association with bone mineral density of the MCP joint.

Statistical analysis

We summarized patient characteristics and outcome variables in the HOA and HC groups as means and SDs for continuous and count data/percentages for categorical variables. HR-pQCT results were analyzed using regression models in three major domains; bone density and microstructure in (i) the MCP2 head, (ii) the distal radius, and (iii) overall bone strength in the distal radius. Density and microstructure measurements from distal
Table 1. Demographic and Clinical Characteristics of Hand Osteoarthritis Patients and Healthy Controls

| Characteristic                  | HOA (n = 29) | HC (n = 76) |
|--------------------------------|--------------|-------------|
| Age (years), means ± SD        | 60.5 ± 6.9   | 55.6 ± 13.3 |
| Females, n (%)                 | 23 (79.3)    | 46 (60.5)   |
| Weight (kg), means ± SD        | 74.7 ± 15.0  | 74.7 ± 16.1 |
| Height (m), means ± SD         | 1.7 ± 0.1    | 1.7 ± 0.1   |
| BMI (kg/m²), means ± SD        | 26.2 ± 4.9   | 24.9 ± 3.8  |
| Current smokers, n (%)         | 3 (10.3)     | 7 (9.2)     |
| ACPA positivity, n (%)         | 0            | 0           |
| RF positivity, n (%)           | 0            | 0           |
| HAQ-DI (units), means ± SD     | 0.84 ± 0.62  | 0.003 ± 0.03|
| SF-SACRAH (units), means ± SD  | 2.6 ± 1.8    | N/A         |
| Stiffness, n (%)               | 20 (69.0)    | 0           |
| Duration stiffness (min), means ± SD | 25.4 ± 57.0  | 0           |
| Arthralgia, n (%)              | 25 (86.2)    | 0           |
| NSAIDs, n (%)                  | 11 (37.9)    | 0           |

All with low to moderate alcohol consumption.

ACPA = anti-cyclic citrullinated protein antibodies; HAQ-DI = health assessment questionnaire disability index; HC = healthy controls; HOA = hand osteoarthritis; N/A = not applicable; NSAID = nonsteroidal anti-inflammatory drug; RF = rheumatoid factor; SF-SACRAH = score for assessment and quantification of chronic rheumatic affections of the hands.

Table 2. Demographic Characteristics of Male and Female Hand Osteoarthritis Patients and Healthy Subjects

| Characteristic                  | HOA (n = 29) | HC (n = 76) |
|--------------------------------|--------------|-------------|
| Age (years), means ± SD        | 59.0 ± 6.5   | 53.1 ± 12.8 |
| Weight (kg), means ± SD        | 71.8 ± 15.4  | 65.4 ± 10.3 |
| Height (m), means ± SD         | 1.7 ± 0.1    | 1.7 ± 0.1   |
| BMI (kg/m²), means ± SD        | 25.9 ± 5.4   | 23.3 ± 3.2  |
| Current smokers, n (%)         | 3 (13.0)     | 5 (10.9)    |
| ACPA positivity, n (%)         | 0            | 0           |
| RF positivity, n (%)           | 0            | 0           |
| HAQ-DI (units), means ± SD     | 0.86 ± 0.64  | 0.005 ± 0.04|
| SF-SACRAH (units), means ± SD  | 2.8 ± 1.8    | N/A         |
| Stiffness, n (%)               | 16 (69.6)    | 0           |
| Duration stiffness (min), means ± SD | 17.3 ± 20.5  | 0           |
| Arthralgia, n (%)              | 22 (79.3)    | 0           |
| NSAIDs, n (%)                  | 10 (43.5)    | 0           |

All with low to moderate alcohol consumption.

ACPA = anti-cyclic citrullinated protein antibodies; HAQ-DI = health assessment questionnaire disability index; HC = healthy control; HOA = hand osteoarthritis; N/A = not applicable; NSAID = nonsteroidal anti-inflammatory drug; RF = rheumatoid factor; SF-SACRAH = score for assessment and quantification of chronic rheumatic affections of the hands.

Results

Demographic and clinical characteristics of osteoarthritis patients and healthy subjects

A total of 105 subjects were included (29 HOA/76 HC) in this study. Detailed demographic and clinical information is presented in Table 1 for HOA and HC groups including stratification for gender (Table 2).
Table 3. Bone Mass, Microstructure, and Biomechanical Properties in the Metacarpal Heads and the Distal Radius

| Properties                        | HOA     | HC     |
|-----------------------------------|---------|--------|
| Bone mass (metacarpal heads)      |         |        |
| Total vBMD (mg HA/cm³)            | 268.3 ± 55.2 | 268.7 ± 45.8 |
| Tb.vBMD (mg HA/cm³)               | 162.5 ± 37.7 | 196.9 ± 34.5 |
| Ct.vBMD (mg HA/cm³)               | 645.9 ± 63.9 | 581.0 ± 77.2 |
| Bone mass (distal radius)         |         |        |
| Total vBMD (mg HA/cm³)            | 259.5 ± 62.5 | 280.0 ± 54.0 |
| Tb.vBMD (mg HA/cm³)               | 139.0 ± 34.8 | 159.2 ± 37.7 |
| MetaTrab.vBMD (mg HA/cm³)         | 195.6 ± 36.0 | 217.7 ± 37.9 |
| InnerTrab.vBMD (mg HA/cm³)        | 100.0 ± 35.8 | 118.8 ± 39.1 |
| Meta/Inn (%)                      | 2.1 ± 0.5 | 2.0 ± 0.7 |
| Ct.vBMD (mg HA/cm³)               | 763.5 ± 68.6 | 776.8 ± 67.5 |
| Bone microstructure (distal radius) |        |        |
| BV/TV (%)                         | 0.11 ± 0.03 | 0.13 ± 0.03 |
| Tb.N (1/mm)                       | 1.9 ± 0.3 | 2.0 ± 0.3 |
| Tb.Th (mm)                        | 0.06 ± 0.01 | 0.07 ± 0.01 |
| Tb.Sp (mm)                        | 0.48 ± 0.10 | 0.44 ± 0.12 |
| Tb./Inn (%)                       | 0.23 ± 0.08 | 0.19 ± 0.07 |
| Ct.Th (mm)                        | 0.60 ± 0.19 | 0.64 ± 0.18 |
| μFEA (distal radius)              |         |        |
| Stiffness (kN/mm)                 | 36.2 ± 10.22 | 44.8 ± 14.7 |
| Failure load (N)                  | 1769.5 ± 451.7 | 2164.4 ± 678.5 |
| Erosions (metacarpal heads)       |         |        |
| Erosions (n)                      | 2.9 ± 2.2 | 1.0 ± 1.3 |
| Osteophytes (n)                   | 3.4 ± 2.9 | 2.2 ± 2.1 |

Decreased trabecular density and increased cortical density in the metacarpal heads in HOA

Unadjusted Tb.vBMD was numerically decreased in patients suffering from HOA (162.5 ± 37.7 versus 196.9 ± 34.5), whereas cortical vBMD values were higher (645.9 ± 63.9 versus 581.0 ± 77.2) (Table 3; gender stratified in Supporting Table S1). In the regression analysis osteoarthritis was independently associated with changes in the multivariate MCP2 outcome matrix (approximated F = 6.65, p < .001). With respect to total effect, estimated marginal means for Z-scores were significantly lower in HOA patients for Tb.vBMD and higher for Ct.vBMD (Table 4), whereas the direct effect was significant only for Ct.vBMD. We did not observe a differential effect of sex (p for interaction = .23). Individual regression models are presented in Supporting Table S2.

Possible gender effect in vBMD and bone microstructure in the distal radius of HOA patients

Total, Tb.vBMD, and Ct.vBMD in the distal radius were numerically lower in patients with HOA compared to HC (Table 3; Fig. 2A,B). At the microstructural level, trabecular number and thickness were also lower, whereas trabecular separation was increased in HOA patients.

However, regression analysis of the multivariate outcome matrix from distal radius did not show an overall significant effect of HOA (approximated F = 1.0, p = .47). The analysis indicates that the observed numerical differences can be explained by differences in sex (approximated F = 14.9, p < .001) and age (approximated F = 6.2, p < .001) and a study group-gender interaction (approximated F = 2.18, p = .044).

A significant gender-study group interaction without a significant main effect of study group indicates either an effect of gender subgroups in opposite directions or a gender subgroup effect with a weight insufficient to make an overall effect significant but an effect size sufficient to make an interaction significant. Among individual linear models (Supporting Table S3), there were gender-study group interactions for radial Tb.vBMD (p = .03) where male HOA patients had a greater absolute reduction than females and for Tb.Th (p = .03) where the differences for male and female HOA patients were in opposite directions (Fig. 1A, Supporting Table S3). Notably, estimated marginal mean Tb.vBMD in the distal radius was lower in males with HOA compared to healthy controls (Δz = −0.9; 95% CI, −1.74 to −0.11), whereas the same difference for females was very small with nearly symmetrical confidence intervals around zero (Table 4).

Radial bone strength is reduced in male but not in female HOA patients

Unadjusted overall mean values of stiffness and failure load were lower in the radius of HOA patients compared to healthy controls (stiffness: 36.2 ± 10.2 versus 45.3 ± 14.7 kN/mm; failure load: 1770 ± 452 versus 2164 ± 679 N) (Table 3). We did not find a significant effect of osteoarthritis in a linear model of failure load after adjusting for age, gender, and smoking status, indicating that failure load was lower in males with HOA compared to male controls, whereas there was no such difference in females (Fig. 2C). This difference, however, was apparent only after adjustment for HAQ (Table 4).

Bone size (cross-sectional area) was comparable between men and women (95% CI, 50.0 mm² ± 2.9 to 2.2). When added, the gender-study group interaction term was not sufficiently precise to make a conclusion based on a conventional significance threshold (p = .06). However, the estimated marginal mean difference for failure load between HOA and controls from this latter model with interactions was −514 N (95% CI, −1084 to −9 N) for males and −1 N (95% CI, −401 to 398 N) for females, indicating that failure load was lower in males with HOA compared to male controls, whereas there was no such difference in females (Fig. 2C). This difference, however, was apparent only after adjustment for HAQ (Table 4).

Erosions, osteophytes, and their association to bone mineral density

In the next step the number of bone erosions and osteophytes in the MCP joints in HOA and HC was analyzed, which revealed that HOA patients had numerically more erosions and osteophytes per patient (Table 3; Fig. 1A,B). We then explored the association of erosions and osteophytes with bone mineral density. The results did not suggest an important association neither between the number of osteophytes and cortical vBMD nor between the number of erosions and trabecular vBMD at the metacarpal head (Supporting Fig. S1). Interobserver agreement for osteophytes (intraclass correlation coefficient [ICC] 0.96; 95% CI, 0.92 to 0.98) and erosions (ICC 0.76; 95% CI, 0.62 to 0.86) was high.
Looking into the literature, interesting observations about the peripheral bone composition in HAO patients have already been reported.30,31 One study in female HAO patients demonstrated an altered phalangeal bone mineral density, which was associated with erosive changes. Another study showed a lower metacarpal index (MCI) and a lower cortical bone index (CCT) in HAO patients. Both studies used plain X-ray or DXA to obtain those density or structural parameters. In contrast, in our study a volumetric approach was used that allows a more accurate distinction between cortical and trabecular bone. The use of high-resolution CT in this study sheds a unique light on the effects of HAO on different bone compartments (intraarticular and periarticular) as well as biomechanical properties in males and females adding new depth of knowledge.

The amount of bone loss in HAO in our study is remarkable given that trabecular bone is degraded to a similar extent as observed in ACPA-positive rheumatoid arthritis (RA).24 Notably, bone loss in HAO is likely to be of local character and hence dissimilar to inflammatory bone loss in RA, which affects the entire skeleton.

For inclusion of patients, we used the 1990 ACR classification criteria.74 These are based on clinical assessment and do not require an additional imaging procedure such as an X-ray or MRI examination. We were surprised to find such a noteworthy decline of trabecular loss accompanied with reduction of biomechanical properties in patients fulfilling these criteria and not having any other systemic rheumatic disease. From a clinical perspective, based on these results we would emphasize to sharpen the awareness of a possible osteoporosis in this group of patients.

Another result of our study is the divergent bone quality in males and females. Male HAO patients showed reduced trabecular vBMD and failure load at the radial bone as opposed to the female HAO cases (Table 4). However, further exploratory work with larger number of patients is necessary to confirm our findings and to better understand the impact of gender in the association of bone quality and HAO.

The mechanism leading to trabecular bone loss of the hand joints and the radius in HAO is not entirely clear; however, it is conceivable that reduced muscle strength, limited mobility, and reduced physical activity, which results from chronic pain and stiffness of HAO, may lead to reduced local bone mass and alter the structure. In accordance with this, general physical impairment measured by HAQ score was significantly higher in HAO as compared to controls. However, the estimated direct effect of HOA on trabecular bone density, after adjustment for HAQ, was not a strong null and only slightly attenuated compared to the null effect in females (Table 4). However, further exploratory work with larger number of patients is necessary to confirm our findings and to better understand the impact of gender in the association of bone quality and HAO.
In contrast to trabecular bone, cortical bone was not reduced in HOA. Although in the hand joints HOA was associated with an increased cortical bone mass, no significant difference between HOA and healthy controls was found at the radius (Table 4, Fig. 1). One can assume that an increase of cortical density and loss of trabecular bone in the metacarpal bone might be a consequence

![Fig. 1. Estimated marginal means in hand osteoarthritis patients and healthy controls. Estimated marginal means of volumetric bone mineral densities for distal radius (A), second metacarpophalangeal head (B) and distal radius failure load (C). Circles depict healthy control group, triangles depict the hand osteoarthritis group. The point estimates and confidence intervals show values estimated using linear regression models including terms for age, sex, study group, study-group sex interaction and functional status. These reflect the estimated means at the overall mean age of the study sample and overall mean HAQ. The results for distal radius vBMD and failure load were stratified by gender due to important gender-study group interactions. Ct = cortical; EMM = estimated marginal means; Inn = inner; kN = kilonewtons; Sp = separation; Tb = trabecular; Th = thickness; vBMD = volumetric bone mineral density.](image)

![Fig. 2. Depiction of a μFEA-derived stress distribution image of HC (A) and HOA (B) participants. Color map labels the von Mises stress (MPa) for described loading scenario. HC = healthy control; HOA = hand osteoarthritis.](image)
of osteophyte and erosion formation. However, we did not observe meaningful relationships between the number of erosions and trabecular bone density or the number of osteophytes and cortical bone density in the metacarpal head (Supporting Fig. S1). This finding indicates that HOA might be uncoupling cortical and trabecular bone metabolism in the intraarticular and periarticular bone with cortical bone being involved in reparative responses during HOA. Another possible explanation for the loss of trabecular bone might in turn follow, such that this reparative response in the cortical bone could lead to an increased cortical area and unload the trabecular compartment. This could in turn lead to trabecular bone loss as a nonspecific bystander phenomenon. However, in contrast to an expected reduction in trabecular bone density with increasing cortical area, our data shows that metacarpal trabecular bone density increases with increasing cortical area in controls but not in HOA patients (Supporting Fig. S1). This observation suggests that the reduced trabecular bone density in osteoarthritic metacarpal bone is possibly beyond simple unloading or shelling caused by cortical thickening per se.

Our study has a number of limitations. We have a small number of male osteoarthritics patients; therefore, the gender interactions described in our study need reproduction and should be interpreted with caution. However, after adjustment for functional impairment, we think it is unlikely that the interactions were caused by a substantial clinical difference between men and women. Another limitation is the use of HAQ as a surrogate for hand function, which may have led to insufficient adjustment for our direct effect estimates.

In summary, this study shows that HOA patients are characterized by a shift from trabecular to cortical bone mass at the functionally relevant MCP2 head and a possible gender effect with male HOA patients having reduced radial trabecular density and thickness in the distal radius. The findings of very substantial deficits in trabecular bone and bone strength could have a possible impact on the routine clinical assessment of fracture risk of HOA patients. Assessment of hand bone mass also represents an interesting possibility to objectify the effect of nonpharmacological and pharmacological approaches in improving function and consequently restoring bone mass in HOA.

Disclosures

The authors have no competing or conflicts of interest.

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All authors have seen and approved the final version of the manuscript. Study conception and design: DS and AK. Acquisition of data: SU, SB, AK, DS, AB, AH, and JR. Analysis and interpretation of data: AK, KT, SU, DS, and GS. Writing of manuscript: AK, DS, KT, and GS. SU’s work was performed in partial fulfillment of the requirements for obtaining a “Dr. med.” (MD) degree.

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