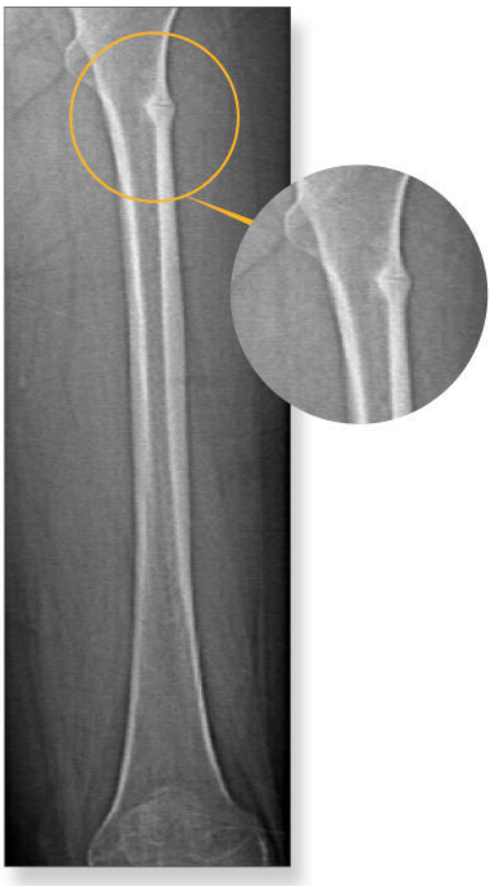
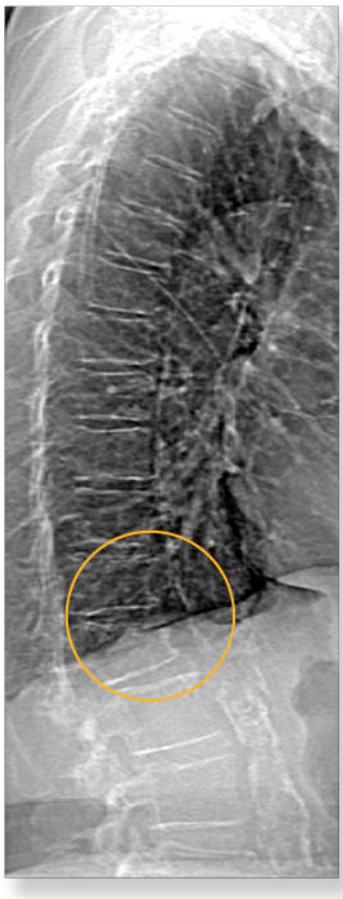
HOLOGIC®
The Science of Sure

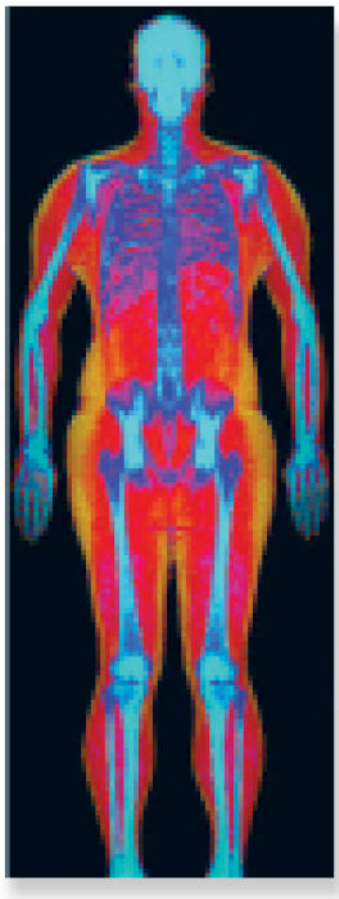
Powerful images.
Clear answers.



Manage Patient's concerns about Atypical Femur Fracture*



Vertebral Fracture Assessment – a critical part of a complete fracture risk assessment



Advanced Body Composition® Assessment – the power to see what's inside

Contact your Hologic rep today at BSHSalesSupportUS@hologic.com

*Incomplete Atypical Femur Fractures imaged with a Hologic densitometer, courtesy of Prof. Cheung, University of Toronto

www.hologic.com | dxaperformance.com | 1.800.442.9892

ORIGINAL ARTICLE

JBMR®

Post-fracture Risk Assessment: Target the Centrally Sited Fractures First! A Substudy of NoFRACT

Tove T Borgen,[1,2] Åshild Bjørnerem,[3,4] Lene B Solberg,[5] Camilla Andreasen,[3,6] Cathrine Brunborg,[7] May-Britt Stenbro,[1] Lars M Hübschle,[8] Anne Froholdt,[9] Wender Figved,[10] Ellen M Apalset,[11,12] Jan-Erik Gjertsen,[13,14] Trude Basso,[15] Ida Lund,[5] Ann K Hansen,[3,6] Jens-Meinhard Stutzer,[16] Tone K Omsland,[17] Lars Nordsletten,[2,5] Frede Frihagen,[5] and Erik F Eriksen[2,18]

[1]Department of Rheumatology, Vestre Viken Hospital Trust, Drammen Hospital, Drammen, Norway
[2]Department of Clinical Medicine, University of Oslo, Oslo, Norway
[3]Department of Clinical Medicine, UiT - The Arctic University of Norway, Tromsø, Norway
[4]Department of Obstetrics and Gynecology, University Hospital of North Norway, Tromsø, Norway
[5]Division of Orthopedic Surgery, Oslo University Hospital, Oslo, Norway
[6]Department of Orthopedic Surgery, University Hospital of North Norway, Tromsø, Norway
[7]Oslo Centre for Biostatistics and Epidemiology, Research Support Services, Oslo University Hospital, Oslo, Norway
[8]Department of Orthopedic Surgery, Vestre Viken Hospital Trust, Drammen Hospital, Drammen, Norway
[9]Department of Physical Medicine, Vestre Viken Hospital Trust, Drammen Hospital, Drammen, Norway
[10]Department of Orthopedic Surgery, Vestre Viken Hospital Trust, Bærum Hospital, Bærum, Norway
[11]Department of Rheumatology, Haukeland University Hospital, Bergen, Norway
[12]Department of Global Public Health and Primary Care, University of Bergen, Bergen, Norway
[13]Department of Orthopedic Surgery, Haukeland University Hospital, Bergen, Norway
[14]Department of Clinical Medicine, University of Bergen, Bergen, Norway
[15]Department of Orthopedic Surgery, St. Olavs University Hospital, Trondheim, Norway
[16]Department of Orthopedic Surgery, Møre and Romsdal Hospital Trust, Molde Hospital, Molde, Norway
[17]Department of Community Medicine and Global Health, Institute of Health and Society, University of Oslo, Oslo, Norway
[18]Department of Endocrinology, Morbid Obesity and Preventive Medicine, Oslo University Hospital, Oslo, Norway

ABSTRACT

The location of osteoporotic fragility fractures adds crucial information to post-fracture risk estimation. Triaging patients according to fracture site for secondary fracture prevention can therefore be of interest to prioritize patients considering the high imminent fracture risk. The objectives of this cross-sectional study were therefore to explore potential differences between central (vertebral, hip, proximal humerus, pelvis) and peripheral (forearm, ankle, other) fractures. This substudy of the Norwegian Capture the Fracture Initiative (NoFRACT) included 495 women and 119 men ≥50 years with fragility fractures. They had bone mineral density (BMD) of the femoral neck, total hip, and lumbar spine assessed using dual-energy X-ray absorptiometry (DXA), trabecular bone score (TBS) calculated, concomitantly vertebral fracture assessment (VFA) with semiquantitative grading of vertebral fractures (SQ1–SQ3), and a questionnaire concerning risk factors for fractures was answered. Patients with central fractures exhibited lower BMD of the femoral neck (765 versus 827 mg/cm^2), total hip (800 versus 876 mg/cm^2), and lumbar spine (1024 versus 1062 mg/cm^2); lower mean TBS (1.24 versus 1.28); and a higher proportion of SQ1-SQ3 fractures (52.0% versus 27.7%), SQ2–SQ3 fractures (36.8% versus 13.4%), and SQ3 fractures (21.5% versus 2.2%) than patients with peripheral fractures (all $p < 0.05$). All analyses were adjusted for sex, age, and body mass index (BMI); and the analyses of TBS and SQ1–SQ3 fracture prevalence was additionally adjusted for BMD). In conclusion, patients with central fragility fractures revealed lower femoral neck BMD, lower TBS, and higher prevalence of vertebral fractures on VFA than the patients with peripheral fractures. This suggests that patients with central fragility fractures exhibit more severe deterioration of bone structure, translating into a higher risk of subsequent fragility fractures and therefore they should get the highest priority in secondary fracture prevention, although attention to peripheral fractures should still not be diminished. © 2019 American Society for Bone and Mineral Research. © 2019 The Authors. *Journal of Bone and Mineral Research* published by American Society for Bone and Mineral Research.

KEY WORDS: BONE MINERAL DENSITY; OSTEOPOROSIS; TRABECULAR BONE SCORE; VERTEBRAL FRACTURE ASSESSMENT; VERTEBRAL FRACTURES

Received in original form May 3, 2019; revised form June 20, 2019; accepted July 8, 2019.

Address Correspondence to: Tove Tveitan Borgen, MD, Department of Rheumatology, Vestre Viken Hospital Trust, Drammen Hospital, N-3004 Drammen, Norway. E-mail: tove.tveitan.borgen@vestreviken.no

Public clinical trial registration: http://clinicaltrials.gov/show/NCT02608801. Prediction and Secondary Prevention of Fractures in a Norwegian Population. A Substudy of Norwegian Capture the Fracture Initiative; and http://clinicaltrials.gov/show/NCT02536898. Norwegian Capture the Fracture Initiative.

Journal of Bone and Mineral Research, Vol. 34, No. 11, November 2019, pp 2036–2044.
DOI: 10.1002/jbmr.3827

Introduction

Fragility fracture is a growing issue worldwide due to longer life expectancies in most populations.[1] The predominant sites of fractures vary with age, and proposed explanations are changes in fall tendency, fall mechanism, and differential loss of cortical and trabecular bone at different stages of aging.[2,3] In clinical assessment after a fragility fracture, the site of fracture adds important information on future fracture risk. In general, a fragility fracture doubles the risk of any subsequent fracture,[4] a hip fracture triples the risk of another hip fracture, and a vertebral fracture increases the risk of subsequent vertebral fracture four to seven times.[4,5] The imminent risk of subsequent fracture is highest the first year after a major osteoporotic fracture (vertebral, hip, distal forearm, proximal humerus) and is more marked in advanced age.[6,7] This constitutes a window of opportunity where antiosteoporotic treatment should be targeted promptly toward patients at highest risk.

The International Osteoporosis Foundation (IOF) recommends assessment of all patients with fragility fractures.[8] Targeting strategies to identify patients at highest risk are warranted to give adequate and timely post-fracture assessment to this large volume of patients. Triaging patients according to fracture types associated with higher or lower expected risk of subsequent fracture could be convenient, especially in areas with limited resources. The major osteoporotic fractures occur at sites that differ with respect to amount and distribution of cortical and trabecular bone. In our Fracture Liaison Service (FLS) clinics, we have observed that patients with fractures at central sites, with abundant trabecular bone (vertebral, hip, proximal humerus, and pelvis), seem to be older and exhibit more pathological features on bone mineral density (BMD), trabecular bone score (TBS), and vertebral fracture assessment (VFA) than patients with fractures at peripheral sites with relatively more cortical bone (forearm, ankle, and other peripheral fractures). This division into central and peripheral fractures diverges from established classifications of fractures such as axial (vertebral, chest, and pelvic) versus appendicular (upper and lower limb) fractures and hip or vertebral versus nonhip nonvertebral fractures. If the clinical observed difference between central and peripheral fractures is significant and persists after adjustment for age and other confounders, this could help to select patients with higher imminent risk of a subsequent fracture first and patients at lower risk second in the FLS model of care.

The objectives of this study were to (i) investigate the risk factors for fractures including BMD, TBS, and proportion of vertebral fracture using VFA in patients with different types of fragility fractures, and (ii) explore the differences between central and peripheral fractures, after adjustment for sex, age, body mass index (BMI), and BMD.

Patients and Methods

Study subjects

NoFRACT is a multicenter study at seven hospitals in Norway with 34976 patients enrolled by January 2019.[9] The objectives of NoFRACT are to investigate the effect on the rate of subsequent fractures of introducing a standardized intervention program consisting of an FLS model of care for identification, assessment, and treatment of osteoporosis in patients with fragility fractures. Eligible for the intervention were women and men aged 50 years or older with any recently diagnosed fragility fracture, except fractures in fingers, toes, and head.[9,10]

This cross-sectional substudy (ClinicalTrials.gov, NCT02608801) of NoFRACT (ClinicalTrials.gov, NCT02536898) included patients at the University Hospital of North Norway, Tromsø, from October 1, 2015, to December 31, 2017, and at the Drammen Hospital from January 1, 2016, to December 31, 2017.[10] During this period, 2682 (>90%) patients above 50 years of age coming to the hospitals with a fragility fracture were identified and offered fracture risk assessment. In most of the elderly inpatients with fractures of the hip, vertebrae, with two or more fragility fractures, or 10-year probability of major osteoporotic fracture ≥20% calculated using the Fracture Risk Assessment Tool (FRAX), the treatment decision was assessed without a dual-energy X-ray absorptiometry (DXA) scan ($n = 1235$). Participants in the substudy were recruited among patients referred to DXA ($n = 1447$) as part of the post-fracture assessment, of whom 58% provided written informed consent ($n = 839$) and 789 had a DXA scan. Of the 789 with a DXA scan, 11 patients had no measurable hips because of metal implants, and one patient was excluded because of poor image quality of the DXA scan. Hence, 777 patients had valid BMD measurement of at least one hip. Of the 785 patients with a DXA scan of the lumbar spine, eight patients were excluded because of less than two evaluable vertebrae. Of the 730 patients who had TBS calculated, 26 patients were excluded due to BMI >37 kg/m^2 (TBS values are not recommended for use in patients with BMI >37 kg/m^2 because of the influence of soft tissue) and 15 patients were excluded because of fractures or anatomical aberrations in two or more vertebrae. Further, only 679 of the patients had lateral thoracolumbar scan for VFA performed. A total of 614 patients had valid BMD measurements of the femoral neck and lumbar spine, VFA, and TBS; 495 women and 119 men. No patients were excluded because of causes known to affect bone metabolism, such as chronic kidney disease ($n = 22$) or use of antiosteoporosis drugs ($n = 39$). The study was approved by The Regional Committee for Medical and Health Research Ethics (REK 2014/2260). To ensure data security a research platform for sensitive data was used.

Variables

The index fractures leading to inclusion were as follows: hip fractures ($n = 41$), vertebral fractures (thoracic and lumbar fractures) ($n = 32$), proximal humerus fractures ($n = 70$), forearm fractures ($n = 247$), ankle fractures ($n = 117$), and other fractures ($n = 107$, including fractures of the pelvis, clavicle, humerus shaft, elbow, hand, distal femur, patella, tibia, and foot). No patients had rib or cervical fractures as index fracture. Vertebral fractures that led to inclusion were diagnosed by X-ray, CT, or MRI, not by VFA. Fracture cases were categorized into groups of index fractures. Based on location and relative proportions of trabecular and cortical bone, we chose to divide fractures into: central fractures (vertebra, hip, proximal humerus, and pelvis) and peripheral fractures (humerus shaft, clavicle, elbow, forearm, hand, distal femur, patella, tibia, ankle, and foot). We also divided the patients into the established groups of axial (spine, chest, and pelvic) versus appendicular (upper or lower limb) fractures. In addition, information on number of previous fractures after the age of 50 years, number of falls during the last 12 months before inclusion, parental history of hip fractures, use of tobacco, diagnosis of rheumatoid arthritis, and use of glucocorticoids was collected through a questionnaire.

Height and weight were measured. BMI was calculated as weight (kg) per square meter height. BMD was measured at the femoral neck and total hip bilaterally and lumbar spine (L_1–L_4)

using DXA (Prodigy Pro; GE Lunar, Madison, WI, USA) in Tromsø and iDXA (Prodigy Pro; GE Lunar, Madison, WI, USA) in Drammen. Phantom quality assurance (QA) of the DXA equipment was performed daily. Lumbar vertebrae with fracture were excluded. BMD *T*-scores were calculated using the Third National Health and Nutrition Examination Survey reference data for white females aged 20 to 29 years.[11] Osteoporosis was defined as femoral neck BMD *T*-score of −2.5 or less, and osteopenia as femoral neck BMD *T*-score between −2.5 and −1.0 according to the diagnosis criteria of the World Health Organization.[12]

TBS was calculated from the lumbar spine (L_1–L_4) DXA scans using TBS iNsight™ software (Medimaps, Geneva, Switzerland) version 3.0.1. Fractured vertebrae were omitted. The European (Medimaps) reference population was used for both sexes. The TBS values were divided into three groups according to estimated fracture risk: high TBS ≥1.31 (low fracture risk), TBS between 1.23 and 1.31 (intermediate fracture risk), and low TBS ≤ 1.23 (high fracture risk).[13]

Images of the lateral thoracolumbar spine (T_4–L_4) were obtained and VFA of the fracture severity was performed using the semiquantitative (SQ) vertebral deformity scoring method by Genant.[10,14] An SQ0 (<20% height loss) was considered as a nonfractured vertebra, SQ1 (20% to 25% height loss) as a mild fracture, SQ2 (25% to 40% height loss) as a moderate fracture, and SQ3 (≥40% height loss) as a severe fracture. Presence of one or more SQ1, SQ2, or SQ3 fractures was termed SQ1–SQ3 fracture and presence of one or more SQ2 or SQ3 fractures was termed SQ2–SQ3 fracture. Patients were also categorized by presence of at least one SQ3 fracture (yes versus no) as a measure of severe deteriorated microarchitecture in trabecular bone. The interobserver agreement of SQ1–SQ3 fractures between two experienced clinicians has shown a κ of 0.84 (95% confidence interval, 0.70 to 0.98).[10]

Statistical analyses

The mean ± SD for the continuous variables and *n* (%) for categorical variables of the characteristics are presented for each of the fracture groups. Continuous variables were checked for normality using quantile-quantile (QQ) plot. The patients were stratified by type of index fracture to show the proportion of patients with osteoporosis at femoral neck, low TBS (TBS ≤ 1.23), and SQ1–SQ3 in the fracture groups. Further, the patients were stratified by age to show the distribution of osteoporosis, osteopenia, and normal BMD at the femoral neck by age and type of fracture. Scatterplot with regression lines of femoral neck BMD, TBS, and proportion of vertebral fractures by 10-year age groups, and vertical lines for the mean age of patients with each type of fractures are shown. Multiple linear regression analyses were used to investigate differences in continuous variables between types of fracture after adjustment for age and sex. Each group was compared to the hip fracture group. This reference group was chosen because fracture of the hip is considered the most serious. Differences between patients with central versus peripheral fractures and axial versus appendicular fractures were assessed using linear regression analyses for continuous variables and Pearson chi-squared test or Fisher's exact test for dichotomous variables. The comparisons of risk factors for fracture between the fracture groups are presented in three models: unadjusted; after adjustment for sex, BMI, and femoral neck BMD; and after an additional adjustment for age. In sensitivity analyses, we compared central fractures versus forearm fractures, central fractures versus peripheral fractures (after exclusion of other fractures), and central (after exclusion of vertebral fractures) versus peripheral fractures, which are shown in Tables S1–S3. To investigate whether the results differed by sex the analyses of central versus peripheral fractures were replicated for women and men separately. Area under the receiver operating characteristic curve (AUC) analyses were performed to explore which of the bone phenotypes was the best to discriminate between the patients with central versus peripheral fractures. Analyses were performed using Stata v15 (version 15; Stata Corporation, Inc., College Station, TX, USA).

Results

Patient characteristics according to fracture types

The majority of the patients were women and 59% of the patients had a fracture of the forearm or ankle (Table 1). Patients with forearm, ankle, and other fractures were younger than those with hip fractures (all $p < 0.01$). BMD at the femoral neck, total hip, and the site with lowest *T*-score was higher in patients with proximal humerus, forearm, ankle, and other types of fractures than those with hip fractures (all $p < 0.05$). The proportion of patients with osteoporosis at the femoral neck was highest in patients with hip fracture (Table 1, Figs. 1 and 2). Mean TBS was higher in patients with other fractures than those with hip fracture (Table 1). BMD and TBS decreased with age, whereas the proportion of patients with SQ1–SQ3 fractures increased (Fig. 3).

Patients with central fractures versus peripheral fractures

One in four patients had sustained a central index fracture (Table 2). Patients with central fractures were older (70.4 versus 64.4 years, $p < 0.001$) exhibited lower BMD at femoral neck, total hip, and at the site with lowest *T*-score (all $p < 0.001$). Those with central fractures also had lower mean TBS (1.24 versus 1.28) and a higher proportion of SQ1–SQ3 fractures (52.0% versus 27.7%), SQ2–SQ3 fractures (36.8% versus 13.4%), and SQ3 fractures (21.5% versus 2.2%) than patients with peripheral fractures after adjustment for sex, BMI, and femoral neck BMD (all $p < 0.05$). These differences in femoral neck BMD, TBS, and proportion of patients with SQ fractures between the central and peripheral fracture groups remained significant after additional adjustment for age. Patients with central fractures were older, exhibited lower BMD at femoral neck and total hip, and a higher proportion of SQ1–SQ3, SQ2–SQ3, and SQ3 fractures than patients with forearm fractures (Table S1) and patients with forearm or ankle fractures (Table S2) (all $p < 0.01$). When patients with vertebral index fractures were excluded from the analyses, patients with central fractures were still older (69.9 versus 64.4 years), exhibited lower BMD at femoral neck and total hip, and a higher proportion of SQ3 fractures (12.5% versus 2.2%) than patients with peripheral fractures (all $p < 0.01$) (Table S3). However, there was no difference in TBS or proportion of SQ1–SQ3 and SQ2–SQ3 fractures between patients with central and peripheral fractures after exclusion of patients with vertebral index fractures. In sex-stratified analyses, we found the same results in the women as in the total cohort, except for lower TBS in those with central versus peripheral fractures after adjustment for age and BMI ($p = 0.003$), but not after additional adjustment for femoral neck BMD ($p = 0.066$) (data not shown). In men, we found no significant difference in femoral neck BMD, TBS, or proportion of SQ1–SQ3 fractures between those with central versus peripheral

Table 1. Characteristics of Patients by Type of Fracture and Compared to Hip Fracture as the Reference Group

Characteristic	Hip	Vertebral	Humerus	Forearm	Ankle	Other
Total patients	41 (6.7)	32 (5.2)	70 (11.4)	247 (40.2)	117 (19.1)	107 (17.4)
Women	27 (65.9)	26 (81.3)	62 (88.6)	218 (88.7)	85 (72.6)	77 (72.0)
Age (years)	70.4 ± 8.3	72.4 ± 6.5	68.7 ± 8.3	64.2 ± 8.1[3]	65.4 ± 8.8[2]	64.6 ± 8.8[3]
BMI (kg/m^2)	24.8 ± 3.2	28.9 ± 4.9	26.9 ± 4.4[2]	26.1 ± 3.8	27.6 ± 3.9[3]	26.3 ± 4.1
Prior fracture	16/32 (50.0)	11/21 (52.4)	29/58 (50.0)	69/189 (36.5)	32/91 (35.2)	41/86 (47.7)
Smoking	1/30 (3.3)	3/23 (13.0)	10/60 (16.7)	23/193 (12.0)	15/98 (15.3)	16/95 (16.8)
Parental hip fracture	7/26 (26.9)	7/18 (38.9)	16/50 (32.0)	43/169 (25.4)	9/78 (11.5)	14/63 (18.2)
Glucocorticoid use	1/31 (3.2)	3/23 (13.0)	3/58 (5.2)	13/197 (6.6)	1/99 (1.0)	6/97 (6.2)
Rheumatoid arthritis	2/31 (6.5)	1/24 (4.2)	4/59 (6.8)	8/197 (4.0)	4/99 (4.0)	2/95 (2.1)
Femoral neck BMD (mg/cm^2)	732 ± 127	757 ± 117	797 ± 106[3]	811 ± 110[3]	846 ± 113[3]	829 ± 122[3]
Femoral neck BMD *T*-score	−2.2 ± 0.9	−2.0 ± 0.9	−1.7 ± 0.8[3]	−1.6 ± 0.8[3]	−1.4 ± 0.8[3]	−1.5 ± 0.9[3]
Normal	4 (9.8)	4 (12.5)	10 (14.3)	44 (17.8)	34 (29.1)	27 (25.2)
Osteopenia	19 (46.3)	19 (59.4)	51 (72.9)	173 (70.0)	75 (64.1)	69 (64.5)
Osteoporosis	18 (43.9)	9 (28.1)	9 (12.9)	30 (12.1)	8 (6.8)[1]	11 (10.3)
Total hip BMD (mg/cm^2)	762 ± 142	788 ± 129	836 ± 117[3]	853 ± 116[3]	907 ± 135[3]	885 ± 146[3]
Total hip BMD *T*-score	−1.9 ± 1.1	−1.8 ± 1.0	−1.4 ± 0.9[3]	−1.2 ± 0.9[3]	−0.8 ± 1.1[3]	−1.0 ± 1.2[3]
Lumbar spine BMD (mg/cm^2)	1060 ± 207	998 ± 183	1014 ± 156	1031 ± 170	1099 ± 171	1091 ± 179
Lumbar spine BMD *T*-score	−1.1 ± 1.7	−1.6 ± 1.5	−1.5 ± 1.3	−1.3 ± 1.4	−0.8 ± 1.4	−0.8 ± 1.4
Lowest BMD *T*-score all sites	−2.4 ± 1.0	−2.5 ± 0.9	−2.1 ± 0.8[1]	−2.0 ± 0.8[1]	−1.7 ± 0.9[3]	−1.8 ± 1.0[2]
Normal	4 (9.8)	2 (6.3)	5 (7.1)	25 (10.1)	22 (18.8)	18 (16.8)
Osteopenia	17 (41.5)	15 (46.9)	41 (58.6)	154 (62.3)	76 (65.0)	65 (60.7)
Osteoporosis	20 (48.8)	15 (46.9)	24 (34.3)	68 (27.6)	19 (16.2)[1]	24 (22.4)
Trabecular bone score	1.25 ± 0.11	1.21 ± 0.10	1.25 ± 0.10	1.28 ± 0.09	1.28 ± 0.11	1.31 ± 0.11[1]
≥1.31	14 (34.1)	5 (15.6)	20 (28.6)	88 (35.6)	49 (41.9)	52 (48.6)
1.23–1.31	12 (29.3)	11 (34.4)	19 (27.1)	86 (34.8)	26 (22.2)	28 (26.2)
≤1.23	15 (36.6)	16 (50.0)	31 (44.3)	73 (29.6)	42 (35.9)	27 (25.2)
SQ1–SQ3 fracture	17 (41.5)	28 (87.5)[3]	28 (40.6)	64 (25.9)	31 (26.5)	39 (36.5)
SQ2–SQ3 fracture	12 (29.3)	26 (81.3)[3]	13 (18.6)	29 (11.7)[2]	16 (13.7)[1]	22 (20.6)
≥1 SQ3 fracture	4 (9.8)	18 (56.3)[3]	7 (10.0)	4 (1.6)[1]	4 (3.4)	6 (5.6)

Values are mean ± SD or *n* (%).

BMD = bone mineral density; BMI = body mass index; SQ = semiquantitative score.

[1] $p < 0.05$, adjusted for sex and age, except the analyses of age, which was only adjusted for sex.

[2] $p < 0.01$, adjusted for sex and age, except the analyses of age, which was only adjusted for sex.

[3] $p < 0.001$, adjusted for sex and age, except the analyses of age, which was only adjusted for sex.

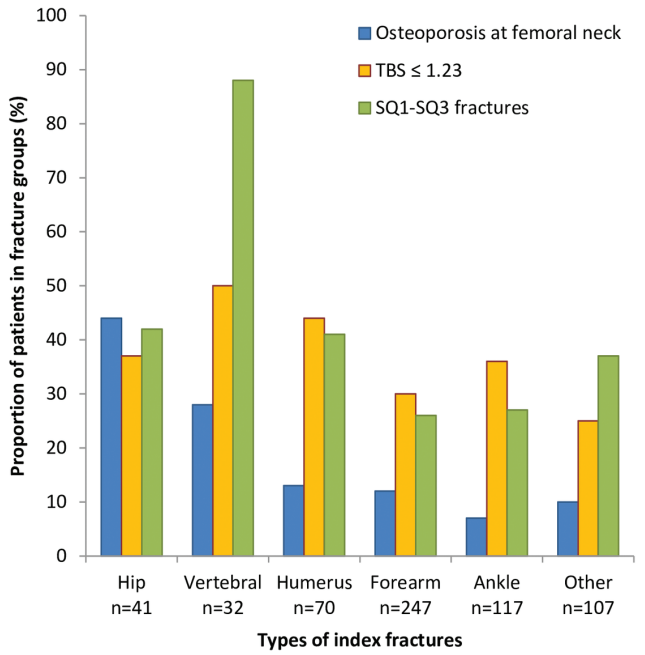


Fig. 1. Proportions of patients with osteoporosis at the femoral neck, low TBS and vertebral fractures (SQ1–SQ3) on vertebral fracture assessment by type of fracture. TBS = trabecular bone score.

fractures after adjusting for age and BMI ($p > 0.05$) (data not shown).

For discrimination of patients with central versus peripheral fractures, the AUC for femoral neck BMD, TBS, and SQ1–SQ3 fractures was 0.644, 0.624, and 0.623, respectively. Adding TBS to femoral neck BMD increased the AUC from 0.644 to 0.663 ($p = 0.300$). Adding SQ1–SQ3 fractures to femoral neck BMD increased the AUC to 0.684 ($p = 0.002$).

Patients with axial fractures versus appendicular fractures

One in 15 patients had an axial index fracture (Table 3). Patients with axial fractures were older (73.2 versus 65.3 years) and exhibited lower BMD at the femoral neck, total hip, and the site with lowest *T*-score after adjustment for age, sex, and BMI (all $p < 0.001$). Those with axial fractures also had lower mean TBS (1.21 versus 1.28) and a higher proportion of SQ1–SQ3 fractures (82.9% versus 30.2%), SQ2–SQ3 fractures (75.9% versus 15.2%), and SQ3 fractures (68.3% versus 8.7%) than those with appendicular fractures after adjustment for sex, BMI, and femoral neck BMD (all $p < 0.05$). All these differences remained statistically significant after additional adjustment for age.

Discussion

In this cohort of subjects with fractures, those with centrally and axially located fractures exhibited lower BMD, lower TBS, and exhibited more SQ1–SQ3, SQ2–SQ3, and SQ3 fractures than those with peripheral and appendicular fractures. These differences remained significant after adjustment for sex, age, BMI, and femoral neck BMD, which supports the notion that intrinsic skeletal properties and localization of fractures are connected.

We propose grouping fragility fractures into central versus peripheral fractures. This emerges from a clinical observation of similarities in patients with these types of fractures, which also is in accordance with the relative proportions of trabecular and cortical bone at these sites. This grouping is a mélange of existing classifications of fractures. The group of central fractures includes both axial and hip/vertebral fractures, in addition to proximal humeral fractures. The group of peripheral fractures consists of mainly forearm and ankle fractures, but also other fractures of the limbs from the diaphysis and distally of the humerus and femur. Patients with central fractures exhibited lower BMD including femoral neck, lower TBS, and a higher prevalence of vertebral fractures, all associated with increased fracture risk,[15–17] than did patients with peripheral fractures.

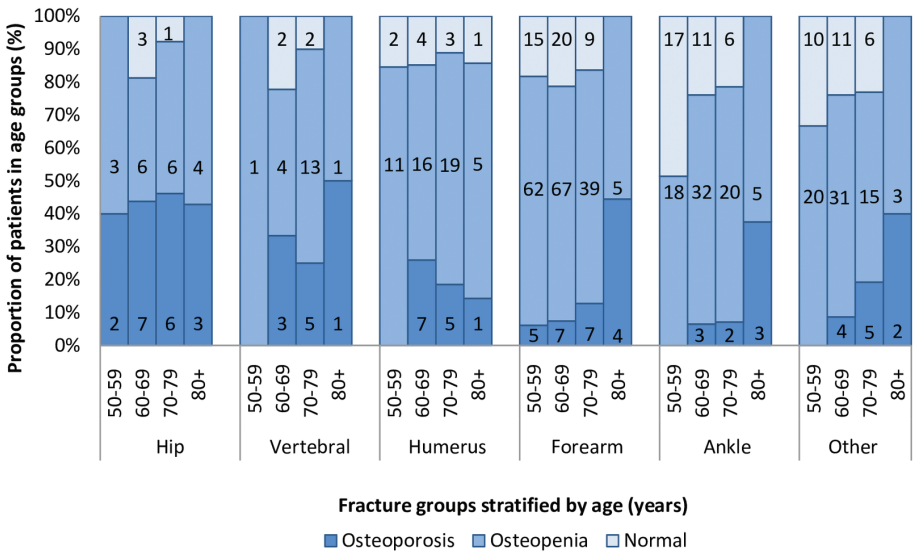


Fig. 2. Proportion and number of patients with osteoporosis, osteopenia, and normal bone mineral density at the femoral neck stratified by types of fracture and in 10-year age groups. Number of patients are shown within each column.

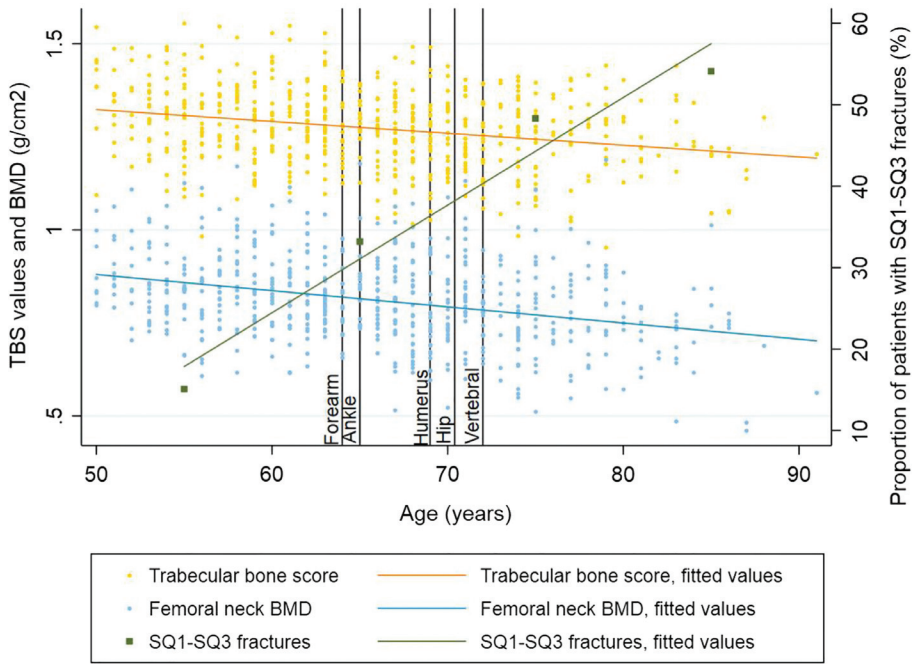


Fig. 3. Fitted lines of TBS and femoral neck BMD and prevalence of SQ1–SQ3 fractures on vertebral fracture assessment in relation to age. BMD = bone mineral density; TBS = trabecular bone score.

Although the difference in TBS and SQ1–SQ3 and SQ2–SQ3 fractures was no longer significant after removing patients with vertebral index fractures, the difference in femoral neck BMD and SQ3 fractures remained. Dividing patients into high-risk and low-risk groups is meaningful, to identify and prioritize the patients at highest risk first for post-fracture assessment in this large volume of patients. These differences were also observed, and also even more marked, when axial fractures were compared to appendicular fractures. Despite this, division into axial and appendicular does not seem to be useful for this purpose, because the group of axial fractures only accounts for 7% of the patients and lacks serious types of fractures such as hip and humerus fractures.

The central fractures are sited in the axial and proximal appendicular part of the skeleton, which encompasses a large proportion of trabecular bone, in most areas exceeding 50%. This was corroborated by our findings of lower TBS in patients with central fractures than in patients with peripheral fractures. Mean TBS, which is a texture index reflecting bone microarchitecture, has been shown to be lower in patients who have sustained fragility fractures compared to fracture-free controls[18,19] and to be lower in patients with than without vertebral fractures on VFA.[10,20] More than one-half of the patients with central fractures in our study had prevalent vertebral fractures on VFA, almost twice the prevalence in the patients with peripheral fractures. This was obviously enhanced by the group of vertebral index fractures. After exclusion of the patients with vertebral fractures, patients with central fractures still exhibited a higher proportion of SQ3 fractures. VFA provides information on trabecular bone strength, because severity of vertebral compressions reflect deterioration of trabecular bone microarchitecture.[21] The patients with central fractures also exhibited lower femoral neck BMD than those with peripheral fractures. Femoral neck BMD can be considered as a proxy of cortical bone strength, because 75% of the bone volume at this site is cortical.[3] Hence, in patients with central fractures, *both* trabecular and cortical bone strength are reduced compared to those with peripheral fractures. Cortical bone architecture is important for fracture propensity, as shown in the Tromsø study.[22] A thinner cortex and increased cortical porosity at the proximal femur were associated with increased risk of fractures.[23] The importance of coexisting cortical and trabecular deterioration for fracture propensity has recently been demonstrated using CT at distal forearm in women.[24,25] Lower femoral neck BMD, lower TBS, and more prevalent vertebral fractures on VFA express lower total bone strength, which in this study is associated with serious fractures like hip and vertebral fractures, fractures that previously have been shown to be associated with increased morbidity and mortality.[26–29]

Prospective studies have shown that low BMD measured at central,[17] as well as peripheral sites,[30,31] predicts any type of fracture. TBS predicts major osteoporotic, clinical vertebral and hip fractures,[19] and vertebral fractures predict new vertebral and nonvertebral fractures.[5,32] We therefore interpret that patients with central fractures, who have lower BMD, lower TBS, and more prevalent vertebral fractures, have a higher risk of future fractures at all sites, including higher imminent fracture risk, than patients with peripheral fractures. However, a peripheral fracture can be an early sign of bone fragility, and with advancing age and bone loss, these patients are expected to have an increased risk of central fractures. Therefore, these patients are also important to assess to prevent future serious major fractures, and the attention to peripheral fractures should not be diminished.

One additional, possible mechanism explaining the differences observed in this study might be falls. In particular in

Table 2. Characteristics of Patients With Central Fractures and Peripheral Fractures

Characteristic	Central fractures	Peripheral fractures	p^1	p^2	p^3
Total patients	152 (24.8)	462 (75.2)			
Women	121 (79.6)	374 (81.0)	0.716	0.079	0.408
Age (years)	70.4 ± 8.1	64.4 ± 8.3	<0.001	<0.001	0.001
BMI (kg/m^2)	26.0 ± 4.2	26.7 ± 4.0	0.125	0.737	0.787
Prior fracture	62/118 (52.5)	136/359 (37.9)	0.005	0.055	0.384
Smoking	15/121 (12.4)	53/377 (14.1)	0.643	0.616	0.925
Falls in the last year	1.3 ± 0.8	1.3 ± 0.8	0.475	0.405	0.443
Parental hip fracture	30/99 (30.3)	66/319 (20.7)	0.047	0.111	0.029
Glucocorticoid use	7/120 (5.8)	20/385 (5.2)	0.786	0.853	0.896
Rheumatoid arthritis	7/122 (5.7)	14/383 (3.7)	0.316	0.288	0.339
Femoral neck BMD (mg/cm^2)	765 ± 118	827 ± 113	<0.001	<0.001	<0.001
Femoral neck BMD *T*-score	−2.0 ± 0.9	−1.5 ± 0.9	<0.001	<0.001	<0.001
Normal	18 (11.8)	105 (22.7)			
Osteopenia	95 (62.5)	311 (67.3)			
Osteoporosis	39 (25.7)	46 (10.0)			
Total hip BMD (mg/cm^2)	800 ± 131	876 ± 129	<0.001	<0.001	<0.001
Total hip BMD *T*-score	−1.7 ± 1.0	−1.0 ± 1.1	<0.001	<0.001	<0.001
Lumbar spine BMD (mg/cm^2)	1024 ± 180	1062 ± 174	0.022	0.030	0.048
Lumbar spine BMD *T*-score	−1.4 ± 1.5	−1.1 ± 1.4	0.022	0.030	0.051
Lowest BMD *T*-score all sites	−2.3 ± 0.9	−1.9 ± 0.9	<0.001	<0.001	0.001
Normal	11 (7.2)	65 (14.1)			
Osteopenia	77 (50.7)	291 (63.0)			
Osteoporosis	64 (42.1)	106 (22.9)			
Trabecular bone score	1.24 ± 0.10	1.28 ± 0.10	<0.001	0.003	0.034
≥1.31	40 (26.3)	188 (22.7)			
1.23–1.31	44 (28.9)	138 (29.9)			
≤1.23	68 (44.8)	136 (29.4)			
SQ1–SQ3 fractures	79 (52.0)	128 (27.7)	<0.001	<0.001	<0.001
SQ2–SQ3 fractures	56 (36.8)	62 (13.4)	<0.001	<0.001	<0.001
≥1 SQ3 fracture	32 (21.5)	10 (2.2)	<0.001	<0.001	<0.001

Values are mean ± SD or *n* (%). Analysis of age was not adjusted for age, analysis of sex was not adjusted for sex, analysis of BMI was not adjusted for BMI, and analysis of BMD was not adjusted for femoral neck BMD.

BMD = bone mineral density; BMI = body mass index; SQ = semiquantitative score.

[1] Unadjusted.

[2] Adjusted for sex, BMI, and femoral neck BMD.

[3] Adjusted for age, sex, BMI, and femoral neck BMD.

relation to hip fractures, but also other peripheral fractures, falls have been invoked to explain fractures in subjects with non-osteoporotic BMD. We found no differences, however, in number of falls during the last 12 months prior to inclusion between patients with central and peripheral fractures (Table 2). Hence, propensity for falls did not influence the type of fracture sustained in this study. We had no detailed information on the mechanism of the falls, which is a possible limitation. There were no differences in number of previous fractures, smoking habits, use of glucocorticoids, or rheumatoid arthritis between the groups. However, more patients with central fractures reported that they had parents with a hip fracture than those with peripheral fractures. After adjustment for covariates, the remaining differences between the patients with central versus peripheral fractures were the intrinsic skeletal properties, assessed using BMD, TBS, and VFA.

To our knowledge, this study is the first to classify patients with fragility fractures into central and peripheral groups. That these two groups of patients differ is intuitive, but showing this and quantifying it with data is novel. However, the study has some limitations. First, only patients in need of a DXA examination who were healthy enough to undergo follow-up were invited to this substudy. This resulted in a selection of healthy patients, with a relatively small proportion of hip fractures. Further, some fracture groups were small. We therefore combined women and men to gain statistical power. The number of men was small and therefore some of our conclusions may not be applicable for men. Finally, the study lacks a control group, and we only measured BMD at central sites. A peripheral measurement could have been of interest to explore whether patients with peripheral fractures would exhibit lower BMD at a peripheral site than patients with central fractures.

In conclusion, patients with fractures at central sites exhibited lower BMD at the femoral neck, total hip, and the site with lowest *T*-score, lower TBS, and higher prevalence of vertebral fractures on VFA than patients with peripheral fractures. These findings indicate that bone loss and deterioration of cortical and trabecular bone structure are important determinants for fractures at these sites. Hence, patients with central fractures are expected to have a higher risk of subsequent fractures. All patients with fragility fractures require secondary fracture assessment, but we propose that patients with central fractures should get the highest priority and be assessed first. This does not imply that the attention to peripheral fractures should be reduced. In recent years, however, new techniques focusing on trabecular bone such as TBS and VFA have emerged, but they are less predictive

Table 3. Characteristics of Patients With Axial Fractures and Appendicular Fractures

Characteristic	Axial fractures	Appendicular fractures	p^1	p^2	p^3
Total patients	41 (6.7)	573 (93.3)			
Women	32 (78.1)	463 (80.8)	0.666	0.171	0.515
Age (years)	73.2 ± 6.7	65.3 ± 8.5	<0.001	<0.001	<0.001
BMI (kg/m^2)	25.7 ± 4.5	26.5 ± 4.0	0.224	0.966	0.990
Prior fracture	17/28 (60.7)	181/449 (40.3)	0.034	0.047	0.445
Smoking	4/31 (12.9)	64/467 (13.7)	0.900	0.901	0.729
Falls in the last year	1.1 ± 0.8	1.3 ± 0.7	0.124	0.099	0.108
Parental hip fracture	7/23 (30.4)	89/395 (22.5)	0.381	0.536	0.303
Glucocorticoid use	3/31 (9.7)	24/474 (5.1)	0.269	0.292	0.306
Rheumatoid arthritis	1/32 (3.1)	20/473 (4.2)	0.893	0.771	0.571
Femoral neck BMD (mg/cm^2)	744 ± 116	816 ± 115	<0.001	<0.001	0.030
Femoral neck BMD *T*-score	−2.1 ± 0.8	−1.6 ± 0.8	<0.001	<0.001	0.031
Normal	4 (9.8)	119 (20.8)			
Osteopenia	25 (61.0)	381 (66.5)			
Osteoporosis	12 (29.2)	73 (12.7)			
Total hip BMD (mg/cm^2)	775 ± 130	863 ± 131	<0.001	<0.001	0.007
Total hip BMD *T*-score	−1.9 ± 1.0	−1.1 ± 1.0	<0.001	<0.001	0.006
Lumbar spine BMD (mg/cm^2)	1007 ± 188	1056 ± 175	0.087	0.095	0.134
Lumbar spine BMD *T*-score	−1.5 ± 1.5	−1.1 ± 1.4	0.079	0.087	0.128
Lowest BMD *T*-score all sites	−2.5 ± 0.9	−1.9 ± 0.9	<0.001	<0.001	0.015
Normal	2 (4.9)	74 (12.9)			
Osteopenia	19 (46.3)	349 (60.9)			
Osteoporosis	20 (48.8)	150 (20.2)			
Trabecular bone score	1.21 ± 0.10	1.28 ± 0.10	<0.001	<0.001	0.040
≥1.31	6 (14.6)	222 (38.7)			
1.23–1.31	13 (31.7)	169 (29.5)			
≤1.23	22 (53.7)	182 (31.8)			
SQ1–SQ3 fractures	34 (82.9)	173 (30.2)	<0.001	<0.001	<0.001
SQ2–SQ3 fractures	31 (75.6)	87 (15.2)	<0.001	<0.001	<0.001
≥1 SQ3 fracture	21 (51.2)	21 (3.7)	<0.001	<0.001	<0.001

Values are mean ± SD or *n* (%). Analysis of age was not adjusted for age, analysis of sex was not adjusted for sex, analysis of BMI was not adjusted for BMI, and analysis of BMD was not adjusted for femoral neck BMD.

BMD = bone mineral density; BMI = body mass index; SQ = semiquantitative score.

[1] Unadjusted.

[2] Adjusted for sex, BMI, and femoral neck BMD.

[3] Adjusted for age, sex, BMI, and femoral neck BMD.

for peripheral fractures. New modalities focusing on cortical bone structure, therefore, remain an unmet medical need.

Disclosures

LBS has received speaker honorarium from Eli Lilly. MBS has received speaker fees from Eli Lilly, Amgen, UCB, and Takeda. WF has received speaker fees from Ortomedic AS and Zimmer Biomet. JMS has received grants for educational activities from BSN Medical. LN has received speaker fees from Novartis, Eli Lilly, and Ortomedic AS. FF has received grants for educational activities from Eli Lilly, Amgen, and Takeda. EFE has received speaker fees from Novartis, Eli Lilly, Amgen, MSD, EffRx, IDS, and Shire. The remaining authors have no conflicts of interest to report.

Acknowledgments

This work was funded by The Regional Health Authorities (243852), The North Norwegian Health Authorities (14083), and Vestre Viken Hospital Trust (1903007). The funders had no role in the design or conduct of the study; in the collection, analyses, and interpretation of the data; or in the preparation, review, or approval of the manuscript. Hanne Louise Hoelstad at Drammen Hospital, and Marit Osima, Anita Kanniainen, and May Greta Pedersen at the Clinical Research Unit, University Hospital of North Norway recruited patients, obtained consents and questionnaires, and performed DXA scans. MediMaps provided temporary license to analyze TBS and Pål Wangen at Scanex helped with calibration of TBS.

Authors' roles

TTB, ÅB, and EFE led the design of this substudy. TTB, ÅB, LBS, TKO, and TB designed the questionnaires. TTB, ÅB, and CA led the patient involvement and data collection. All authors contributed to methodological decisions, data interpretation, conclusions, and dissemination. TTB and CB performed the statistical analysis; TTB drafted the initial manuscript and is responsible for the data integrity. All authors contributed to drafting of the manuscript, contributed, and approved the final manuscript. ÅB is the chief investigator leading protocol development, approvals, and dissemination. LN is the guarantor.

References

1. Oden A, McCloskey EV, Kanis JA, Harvey NC, Johansson H. Burden of high fracture probability worldwide: secular increases 2010-2040. Osteoporos Int. 2015;26(9):2243–8.
2. Nevitt MC, Cummings SR. Type of fall and risk of hip and wrist fractures: The study of osteoporotic fractures. The Study of Osteoporotic Fractures Research Group. J Am Geriatr Soc. 1993;41(11):1226–34.
3. Woolf AD, Åkesson K. Osteoporosis. London: Clinical Publishing; 2008 p 160 (Atlas of Investigation and Management).
4. Klotzbuecher CM, Ross PD, Landsman PB, Abbott TA 3rd, Berger M. Patients with prior fractures have an increased risk of future fractures: a summary of the literature and statistical synthesis. J Bone Miner Res. 2000;15(4):721–39.
5. Gehlbach S, Saag KG, Adachi JD, et al. Previous fractures at multiple sites increase the risk for subsequent fractures: the Global Longitudinal Study of Osteoporosis in Women. J Bone Miner Res. 2012;27(3):645–53.
6. Johansson H, Siggeirsdottir K, Harvey NC, et al. Imminent risk of fracture after fracture. Osteoporos Int. 2017;28(3):775–80.
7. Roux C, Briot K. Imminent fracture risk. Osteoporos Int. 2017;28(6): 1765–9.
8. Akesson K, Marsh D, Mitchell PJ, et al. Capture the fracture: a best practice framework and global campaign to break the fragility fracture cycle. Osteoporos Int. 2013;24(8):2135–52.
9. Andreasen C, Solberg LB, Basso T, et al. Effect of a fracture liaison service on the rate of subsequent fracture among patients with a fragility fracture in the Norwegian capture the fracture initiative (NoFRACT): a trial protocol. JAMA Netw Open. 2018;1(8):e185701.
10. Borgen TT, Bjornerem A, Solberg LB, et al. High prevalence of vertebral fractures and low trabecular bone score in patients with fragility fractures: a cross-sectional sub-study of NoFRACT. Bone. 2019;122:14–21.
11. Kanis JA, Adachi JD, Cooper C, et al. Standardising the descriptive epidemiology of osteoporosis: recommendations from the Epidemiology and Quality of Life Working Group of IOF. Osteoporos Int. 2013; 24(11):2763–4.
12. Kanis JA, McCloskey EV, Harvey NC, Johansson H, Leslie WD. Intervention thresholds and the diagnosis of osteoporosis. J Bone Miner Res. 2015;30(10):1747–53.
13. McCloskey EV, Oden A, Harvey NC, et al. A meta-analysis of trabecular bone score in fracture risk prediction and its relationship to FRAX. J Bone Miner Res. 2016;31(5):940–8.
14. Genant HK, Wu CY, van Kuijk C, Nevitt MC. Vertebral fracture assessment using a semiquantitative technique. J Bone Miner Res. 1993;8 (9):1137–48.
15. Black DM, Arden NK, Palermo L, Pearson J, Cummings SR. Prevalent vertebral deformities predict hip fractures and new vertebral deformities but not wrist fractures. Study of Osteoporotic Fractures Research Group. J Bone Miner Res. 1999;14(5):821–8.
16. Schousboe JT, Vo T, Taylor BC, et al. Prediction of incident major osteoporotic and hip fractures by trabecular bone score (TBS) and prevalent radiographic vertebral fracture in older men. J Bone Miner Res. 2016;31(3):690–7.
17. Stone KL, Seeley DG, Lui LY, et al. BMD at multiple sites and risk of fracture of multiple types: long-term results from the Study of Osteoporotic Fractures. J Bone Miner Res. 2003;18(11):1947–54.
18. Pothuaud L, Barthe N, Krieg MA, Mehsen N, Carceller P, Hans D. Evaluation of the potential use of trabecular bone score to complement bone mineral density in the diagnosis of osteoporosis: a preliminary spine BMD-matched, case-control study. J Clin Densitom. 2009;12(2): 170–6.
19. Hans D, Goertzen AL, Krieg MA, Leslie WD. Bone microarchitecture assessed by TBS predicts osteoporotic fractures independent of bone density: the Manitoba study. J Bone Miner Res. 2011;26(11):2762–9.
20. Nassar K, Paternotte S, Kolta S, Fechtenbaum J, Roux C, Briot K. Added value of trabecular bone score over bone mineral density for identification of vertebral fractures in patients with areal bone mineral density in the non-osteoporotic range. Osteoporos Int. 2014;25(1): 243–9.
21. Genant HK, Delmas PD, Chen P, et al. Severity of vertebral fracture reflects deterioration of bone microarchitecture. Osteoporos Int. 2007;18(1):69–76.
22. Ahmed LA, Shigdel R, Joakimsen RM, et al. Measurement of cortical porosity of the proximal femur improves identification of women with nonvertebral fragility fractures. Osteoporos Int. 2015;26(8): 2137–46.
23. Shigdel R, Osima M, Lukic M, et al. Determinants of transitional zone area and porosity of the proximal femur quantified in vivo in postmenopausal women. J Bone Miner Res. 2016;31(4):758–66.
24. Zebaze R, Atkinson EJ, Peng Y, et al. Increased cortical porosity and reduced trabecular density are not necessarily synonymous with bone loss and microstructural deterioration. JBMR Plus. 2018;3(4): e10078.
25. Bala Y, Zebaze R, Ghasem-Zadeh A, et al. Cortical porosity identifies women with osteopenia at increased risk for forearm fractures. J Bone Miner Res. 2014;29(6):1356–62.
26. Omsland TK, Emaus N, Tell GS, et al. Mortality following the first hip fracture in Norwegian women and men (1999–2008). A NOREPOS study. Bone. 2014;63:81–6.
27. Abrahamsen B, van Staa T, Ariely R, Olson M, Cooper C. Excess mortality following hip fracture: a systematic epidemiological review. Osteoporos Int. 2009;20(10):1633–50.
28. Fink HA, Ensrud KE, Nelson DB, et al. Disability after clinical fracture in postmenopausal women with low bone density: the fracture intervention trial (FIT). Osteoporos Int. 2003;14(1):69–76.
29. Morin S, Lix LM, Azimaee M, Metge C, Caetano P, Leslie WD. Mortality rates after incident non-traumatic fractures in older men and women. Osteoporos Int. 2011;22(9):2439–48.
30. Siris ES, Miller PD, Barrett-Connor E, et al. Identification and fracture outcomes of undiagnosed low bone mineral density in postmenopausal women: results from the National Osteoporosis Risk Assessment. JAMA. 2001;286(22):2815–22.
31. Siris ES, Brenneman SK, Barrett-Connor E, et al. The effect of age and bone mineral density on the absolute, excess, and relative risk of fracture in postmenopausal women aged 50–99: results from the National Osteoporosis Risk Assessment (NORA). Osteoporos Int. 2006;17(4):565–74.
32. Delmas PD, Genant HK, Crans GG, et al. Severity of prevalent vertebral fractures and the risk of subsequent vertebral and nonvertebral fractures: results from the MORE trial. Bone. 2003;33(4):522–32.