Clinical Diagnostic Tools of Osteoporosis: Vertebral Fracture Assessment and Measurement of Bone Mineral Density (BMD)

Masako Ito

Keywords

Vertebral fracture · Quantitative morphometric (QM) approach · Semiquantitative (SQ) approach · Bone mineral density (BMD) · Dual-X-ray absorptiometry (DXA) · Quantitative computed tomography (QCT) · Trabecular microstructure Bone geometry · Finite element analysis (FEA)

1 Vertebral Fracture Assessment

Diagnosis of vertebral fractures requires a standard definition to evaluate the degree of reduction in vertebral body height compared to normal. Conventional lateral radiographs including from Th4 through L4 are required. Anteroposterior view radiographs are sometimes useful to define a complicated shape, such as with a hemi-collapsed vertebral body or huge osteophytes. Both quantitative (morphometric) (QM) and semiquantitative (visual) (SQ) techniques [1, 2] are used to assess prevalent as well as incident fractures on radiographs.

A "morphological fracture" is diagnosed when a vertebral fracture is observed on radiographs, regardless of the presence or absence of clinical symptoms. "Clinical fractures" are suspected by clinically obvious symptoms, such as low back pain, and then confirmed on radiographs.

The present invited review was completed and submitted to the publisher on 05-Sep-19.

M. Ito (✉)
Trustee, Nagasaki University, Nagasaki, Japan
e-mail: masako@nagasaki-u.ac.jp

H. E. Takahashi et al. (eds.), *Osteoporotic Fracture and Systemic Skeletal Disorders*, https://doi.org/10.1007/978-981-16-5613-2_10

Vertebral deformities need not be classified as "wedge," "crush", or "biconcave," since this classification does not seem to improve the correlation with bone mass or clinical manifestations of vertebral fractures.

1.1 Clinical Significance of Vertebral Fracture Assessment

Recognizing the presence of vertebral fractures is important to diagnose osteoporosis, and the severity (number and grade) of vertebral fractures has a strong relationship with the severity of osteoporosis. Therefore, vertebral fracture assessment, as well as bone density measurement, is an essential tool in the diagnosis of osteoporosis. Furthermore, observation of incident and/or worsening vertebral fractures on consecutive radiographs in patients treated with anti-osteoporotic agents is useful to evaluate the effects of therapy.

The following study presented evidence that SQ grading predicts the risk of vertebral and nonvertebral fractures. In the randomized, double-blind, 3-year, Multiple Outcomes of Raloxifene Evaluation (MORE) trial, 7705 postmenopausal women with osteoporosis (low BMD or prevalent vertebral fractures) were randomly assigned to placebo, raloxifene 60 or 120 mg/day [3]. Post hoc analyses showed the association between baseline fracture severity and new fracture risk in the placebo group based on the SQ approach. In women without prevalent vertebral fractures, 4.3% and 5.5% had new vertebral and nonvertebral fractures, respectively. In women with mild, moderate, and severe prevalent vertebral fractures, 10.5%, 23.6%, and 38.1%, respectively, had new vertebral fractures, whereas 7.2%, 7.7%, and 13.8%, respectively, had new nonvertebral fractures.

1.2 Prevalent Fractures

The observation of one or more vertebral fractures at one point in time on radiographs means that one or more vertebral fractures likely occurred earlier.

Deformities of vertebral bodies can result from several disorders, including fractures, degenerative or malignant diseases, congenital abnormalities, and anatomical variants. Before a clinical diagnosis of vertebral fracture is made, these alternative diagnoses should be considered. Vertebral deformities may be detected by qualitative readings, by morphometric measurements, or by a combination of the two approaches.

1.2.1 Quantitative Morphometry (QM) for Prevalent Fractures

Each vertebra should be marked with points, with careful location and labeling of the vertebral level. Six points are marked, defining the anterior (Ha), middle (Hm), and posterior (Hp) heights of each vertebral body (Fig. 1). The points should be placed to take into account parallax in the projection of the endplate and posterior elements.

1.2.2 Semiquantitative (SQ) Approach for Prevalent Fractures

With no measurement of vertebral height, deformity grading is performed visually. The definition of fracture should include deformities of the endplates and anterior

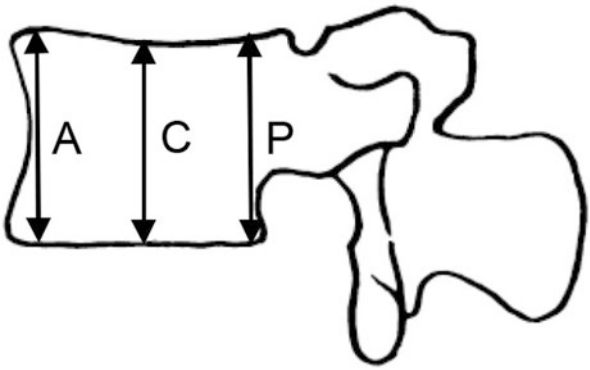

Fig. 1 Quantitative morphometry approach to evaluate vertebral fracture. Six points are marked, defining the anterior (Ha), middle (Hm), and posterior (Hp) heights of each vertebral body. The ratios of Ha/Hp, Hm/Hp, and Hp/Hp‘ are calculated to evaluate the deformity. p‘: posterior height of the neighboring vertebra

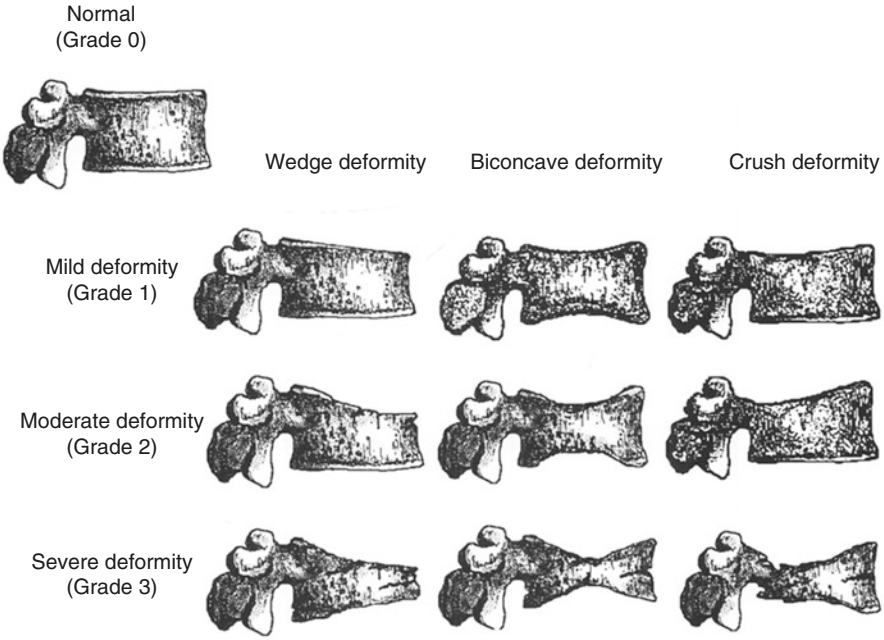

Fig. 2 Semiquantitative approach for vertebral fracture grading. Based on normal (grade 0), grade 1 is about a 20–25% reduction in vertebral height (leading anterior, middle, and posterior heights), grade 2 is about 25–40%, respectively, and grade 3 is a decrease of about 40% or more [1]

borders of vertebral bodies, as well as the generalized collapse of a vertebral body. Based on normal (grade 0), grade 1 is about a 20–25% reduction in vertebral height (leading anterior, middle, and posterior heights), grade 2 is about 25–40%, and grade 3 is a decrease of about 40% or more. Grade 1 or higher is judged as a vertebral fracture (Figs. 2 and 3).

An atlas of standard films and illustrations may help to ensure consistency (Fig. 2).

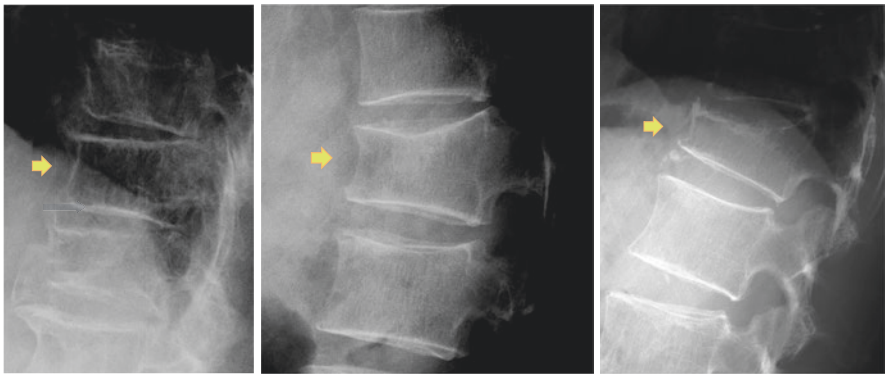

Fig. 3 Worsening fracture (Grade 1 to 3). Grade 1 is a minor change, which can be judged by comparison with the upper and lower vertebral bodies

1.3 Incident Fractures

Substantial reductions in the height of a vertebral body over a relatively short period of time can be diagnosed as an incident fracture. To assess incident fractures, before and after films are compared to detect changes in vertebral morphology or measurements. Procedures for obtaining qualitative and quantitative assessments of incident fractures may be the same as for prevalent fractures.

1.3.1 Quantitative Morphometry (QM) for Incident Fractures

The height reduction (mm) or percentage changes in height (%) are calculated based on the Ha, Hm, and Hp in consecutive lateral radiographs.

There are the following problems in the assessment of incident fractures using the QM approach. First, the best definition has not been established. Some studies have defined a new fracture or deformity as a ≥15% reduction in any one of the three measured vertebral heights (Ha, Hm, or Hp). More stringent criteria, such as a ≥20% change or a change exceeding three standard deviations of the mean difference for that vertebral level, may reduce the number of false-positive results.

It is problematic to define fractures based on percentage changes in height of already deformed vertebrae. Measurements are more difficult on vertebral bodies that are already deformed, and smaller absolute changes in heights will produce larger percentage changes.

1.3.2 Semiquantitative (SQ) Approach for Incident Fractures

The SQ approach has been used in several randomized and blinded clinical trials that have found therapeutic effects.

If grade 0 changes to grade 1, 2, or 3 during follow-up, it is diagnosed as a new fracture, and if grade 1 changes to grade 2 or 3 or grade 2 changes to grade 3, it is diagnosed as a worsening fracture (Fig. 4). Grade 3 remains grade 3 even if vertebral body deformation progresses. Also, the case in Fig. 5 shows the progression of deformity from grade 2 to grade 3 due to fracture healing, not a worsening of a fresh fracture.

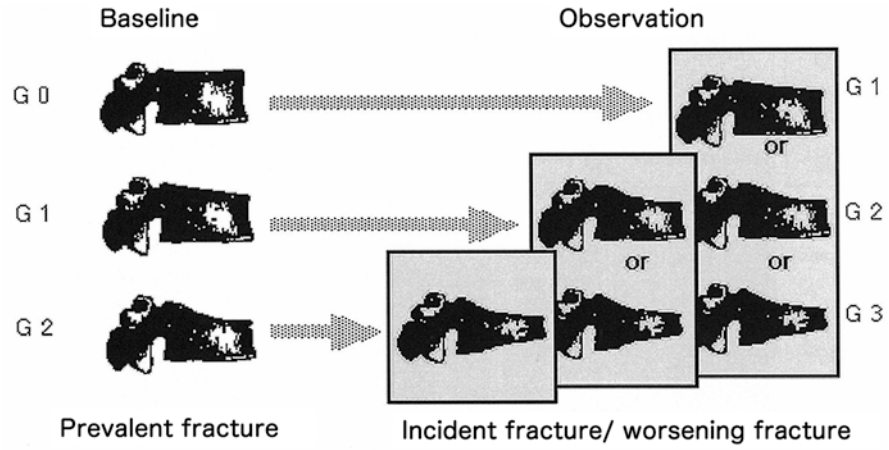

Fig. 4 Diagnosis of incident or worsening fractures using the SQ approach. If grade 0 changes to grade 1, 2, or 3 during follow-up, it is diagnosed as a new fracture, and if grade 1 changes to grade 2 or 3 or grade 2 changes to grade 3, it is diagnosed as a worsening fracture

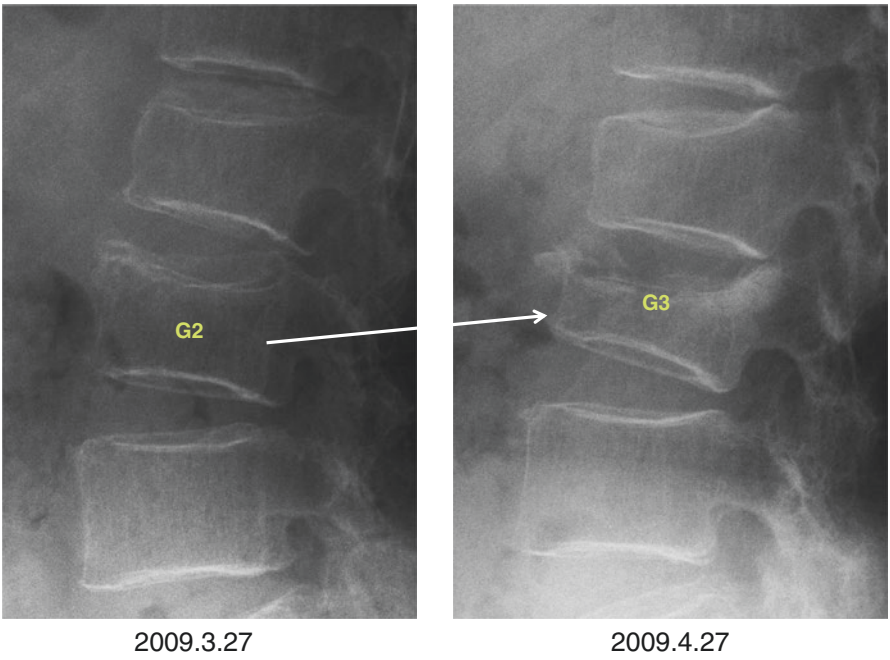

Fig. 5 A case of fracture healing mimics worsening fracture

As mentioned before, baseline vertebral fracture severity assessed using the SQ approach was the best independent predictor for new vertebral and nonvertebral fracture risk [3].

1.3.3 Comparison of SQ and QM Approaches

Morphometry is describable and reproducible. It may be useful for classifying vertebral deformities that are considered uncertain or "mild" by qualitative readings.

The superiority of the SQ method is that it is not affected by variations due to imaging, and basically, it is not affected by the patient's positioning or image magnification as the QM method is. So that, the reproducibility is improved in order to capture the deformation of the vertebral body as the spectrum of the entire vertebral body image. Since pointing, scaling, and calculating are not necessary, the processing time can be kept short. Knowledge of normal variations and interpretation training (experience) are required. Since intra- and interobserver variations are a well-recognized problem in clinical radiology, an excellent agreement can be achieved by extensive training and the use of clear protocols for assessment.

The comparison between QM and SQ assessments in the clinical trial suggested that one QM approach produced similar results as an SQ method [4]. A consensus on the usefulness of SQ assessment of vertebral fractures as a standardized method has been established.

1.3.4 Combination of SQ and QM

To compare visual SQ and QM approaches for assessing prevalent and incident vertebral fractures in postmenopausal osteoporosis, 503 women (age $\geq$ 65 years) were randomly selected from the Study of Osteoporotic Fractures (SOF) population [5]. SQ and QM approaches and their combination were used. This study concluded that QM had limited ability to detect mild fractures, but good ability to detect moderate/severe fractures, as classified by SQ. The use of a combination of sensitive SQ and QM criteria, with adjudication by an experienced radiologist, showed the relative strengths of each of the methods. QM should not be performed in isolation, particularly when applying highly sensitive morphometric criteria at low threshold levels without visual assessment to confirm the detected prevalent or incident vertebral deformity.

2 Measurement of Bone Mineral Density (BMD)

Osteoporosis is significantly related to bone fragility and consequent fractures. Therefore, the diagnosis and monitoring of osteoporosis using bone mineral density (BMD) measurement are important tools in the clinical aspects of osteoporosis, as well as the assessment of vertebral fractures. The World Health Organization (WHO) proposed guidelines for the diagnosis of osteoporosis based on BMD measurement using dual X-ray absorptiometry (DXA) in 1994 [6]. Since then, DXA has been widely used in epidemiological studies, clinical research, and osteoporosis treatment strategies. QCT had been used in the 1980s [7] and is also recommended by the WHO as an acceptable method in the diagnosis of osteoporosis.

2.1 Dual X-ray Absorptiometry (DXA)

Dual X-ray absorptiometry (DXA) is the gold standard for measuring areal BMD (g/cm^2), mainly in the lumbar spine and proximal femur. Low-dose X-rays with two distinct energy peaks through the bones are examined. The value of BMD is derived based on the different absorption rates of dual X-ray energy by soft tissue and by bone. DXA makes the diagnosis of osteoporosis, is helpful for monitoring BMD, and is used for the prediction of fracture risk.

The advantages of DXA are: (1) high precision, (2) low exposure dose, (3) BMD measurement correlates with fracture risk, and (4) easy to operate. On the other hand, the problem with it is the limits derived from two-dimensional measurement: (1) it reflects the size of one bone, in other words, large bones overestimate bone density, small bones underestimate it, (2) it cannot exclude elements overlapping the bone (such as aortic calcification) from the bone evaluation area, and (3) evaluation of cancellous bone and cortical bone cannot be performed separately.

Although there are limitations as described above, the benefits greatly exceed them, and this is an essential examination in osteoporosis medical care.

2.1.1 Skeletal Sites to Measure

Standard measurement sites are both the posterior-anterior (PA) spine and the proximal femur.

Forearm BMD should be measured under the following circumstances: (1) hip and/or spine cannot be measured or interpreted, (2) hyperparathyroidism, and (3) very obese patients (over the weight limit for the DXA table).

2.1.2 Lumbar Spine DXA

A region of Interest (ROI) is defined in PA L1-L4 (or L2-L4). BMD values are measured in all evaluable vertebrae (Fig. 6), only excluding vertebrae affected by local structural change or artifact. A BMD-based diagnostic classification should not be

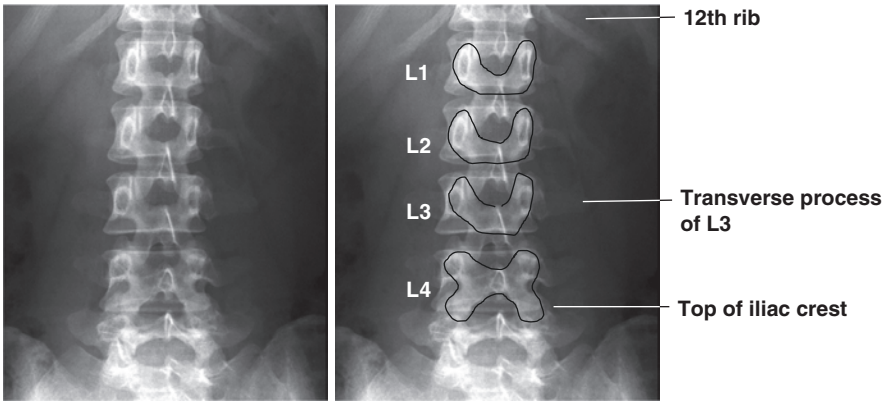

Fig. 6 How to define the vertebral level in Lumbar DXA. Basically, the identification of the ribs and iliac crest is confirmed to determine the level of the vertebral body. Another useful clue is that the longest transverse process is in L3 and the posterior component of L1-3 is U-shaped, and L4 is X-shaped for reference

made using a single vertebra. If only one evaluable vertebra remains after excluding other vertebrae, the diagnosis should be based on a different valid skeletal site.

DXA is of limited use in subjects with a spinal deformity or those who have had previous spinal surgery. The presence of vertebral compression fractures or osteoarthritis has an effect on the accuracy of the measurement.

Anatomically abnormal vertebrae may be excluded from analysis if: (1) they are visually abnormal and non-assessable within the resolution of the system, (2) there is more than a 1.0 T-score difference between the vertebra in question and adjacent vertebrae, and (3) the lateral spine should not be used for diagnosis.

2.1.3 Proximal Femur DXA

In the proximal femur, four different ROIs are defined; femoral neck, trochanter, Ward's triangle, the shaft, and the total hip (Fig. 7). The total hip includes the neck, trochanter, and shaft regions. For the diagnosis of osteoporosis, BMD values in the neck or total hip are used, and for monitoring, BMD in the neck and total hip are used, with the total hip being preferable. Ward's triangle should not be used both for diagnosis and monitoring.

2.1.4 Interpretation of DXA Results

DXA BMD results are interpreted according to two scores.

T-score: The amount of BMD compared with the young adult mean (peak bone mass) of the same sex. T-score is calculated as this differs from the average value divided by the standard deviation (SD). A score of −1 and above is considered normal. A score between −1.1 and −2.4 is classified as osteopenia (low bone mass). A

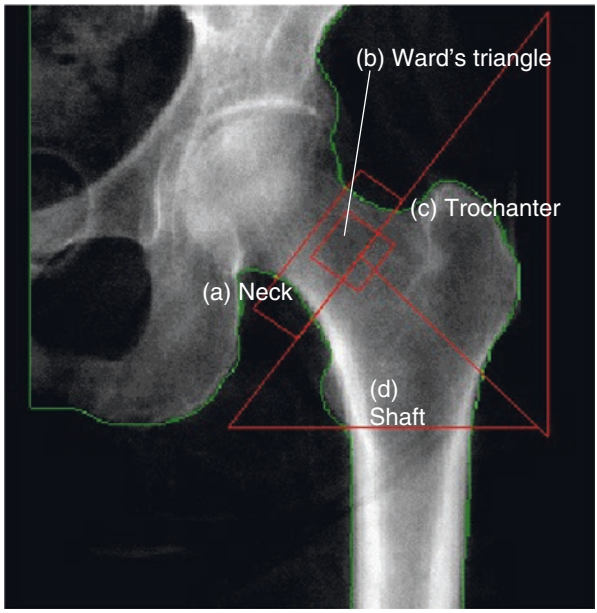

Fig. 7 Regions of BMD measurement in the proximal femur. (**a**) femoral neck (b) Ward's triangle (**c**) trochanter and (**d**) shaft. The proximal femur is the combined area of (**a**), (**c**), and (**d**)

score of −2.5 and below is defined as osteoporosis. The T-score is used to estimate the fracture risk and determine if treatment is required.

Z-score: The amount of bone compared with subjects of the same age and sex. Z-score is calculated as this differs from the average value divided by the SD. If this score is unusually high or low, further medical examinations are required. For evaluation in females prior to menopause and in males younger than age 50 years, Z-scores (not T-scores) are preferred to evaluate bone health.

2.1.5 Monitoring Using DXA

Follow-up DXA exams should be performed at the same institution and ideally with the same machine. BMD measurements obtained with different DXA machines cannot be directly compared.

The BMD value is used to evaluate the treatment effect after administration of anti-osteoporotic agents, using the percentage change rate. The change of the T-score is not used for the evaluation.

Whether a change in BMD values is significant or within an error range is judged based on the least significant change (LSC = CV × 1.96 × $\sqrt{2}$, CV: coefficient of variation). If the BMD is less than the LSC, it is necessary to evaluate it as non-response, re-examine the treatment, and examine for the presence or absence of secondary osteoporosis, but if the treatment period is too short, an accurate response cannot be captured. Although the measurement interval varies depending on the individual case, it is usually measured 1 year after the start of treatment. However, if rapid bone loss is predicted, such as during glucocorticoid treatment, the interval needs to be shortened.

The best skeletal site for monitoring is the lumbar spine, because it is the site with the highest treatment sensitivity and high measurement precision.

If the patient is not properly positioned, re-measurements will be required. On follow-up observation, based on the information of the first measurement result, it is important to make the size and the position of the ROI uniform. Using the comparative analysis function, the usefulness of the copy ROI at the same site as before is established.

2.2 Quantitative Computed Tomography (QCT)

Quantitative computed tomography (QCT) offers superior sensitivity in diagnosing osteoporosis, monitoring bone density changes, and evaluating bone trabecular microarchitectural and mechanical properties simultaneously, but it is still considered a supplemental method due to the high radiation exposure. Two-dimensional QCT-BMD measurement of the spine has tended to show a lower precision, which leads to its limited use, but three-dimensional QCT-BMD provides higher precision and is used for the analysis of the proximal femur, as well as the lumbar spine.

QCT also provides volumetric BMD (mg/cm^3), mainly in the lumbar spine and proximal hip. Since QCT provides three-dimensional data, individual BMD values are obtained in the trabecular and cortical components.

2.2.1 QCT Technique in the Lumbar Spine

A CT image is obtained using standard scan parameters in the lumbar spine with a calibration phantom under the patient's back (Fig. 8). A lower radiation dose protocol is used, such as 80 kVp/140 mAs or 140 kVp/80 mAs, with an image thickness of 5 mm or greater. The calibration phantom technique has two functions, translating the Hounsfield unit (CTHU) to the bone units (mg/mm^3) and calibrating CTHU within the location, using the calibration phantom, which contains different concentrations of calcium (hydroxyapatite) in the rods. The lumbar trabecular bone and the phantom rods at the center area (L1–L4 or L1–L3) can be segmented semi-automatically by computer.

Currently, the whole vertebral body is scanned using multi-detector row CT (MDCT).

2.2.2 Hip BMD Measurement by CT Two-Dimensional Projection Images

QCT X-Ray Absorptiometry (CTXA) analysis at the hip using pelvis CT images with a calibration phantom and software system (Fig. 9) was developed by Cann et al. (Mindways Software, Inc., Austin, TX) [8]. This technique uses a

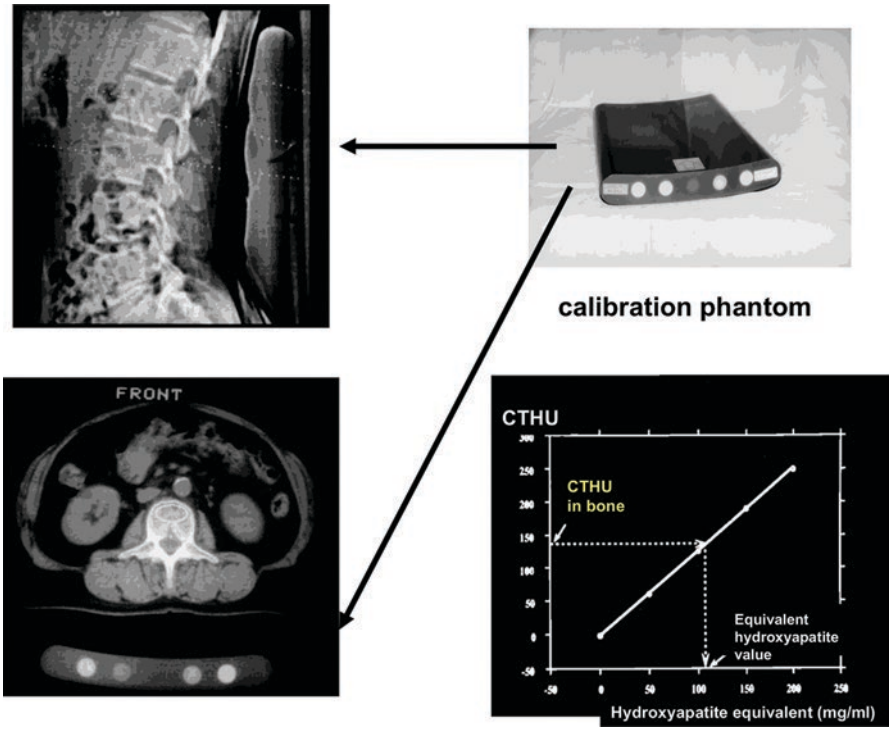

Fig. 8 Quantitative computed tomography (QCT). CT image is obtained using standard scan parameters in the lumbar spine with a calibration phantom under the patient's back. The calibration phantom translates the Hounsfield unit (CTHU) to the bone units (mg/mm^3). According to the linear relationship between hydroxyapatite equivalent (mg/ml) and CTHU, bone mineral density (mg/mm^3) of the trabecular bone is calculated

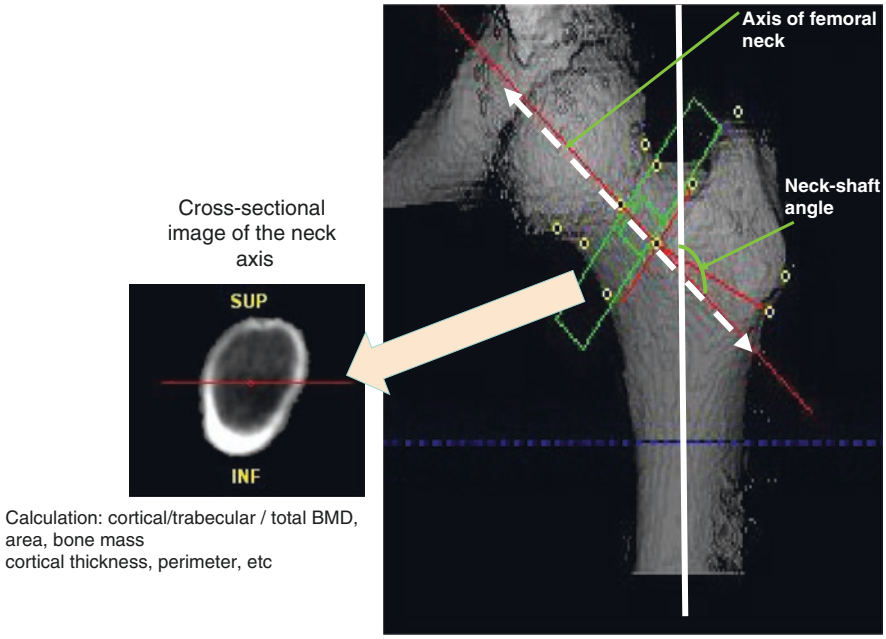

Fig. 9 Hip BMD and structure analysis using three dimensional (3D)-QCT. Using reconstructed 3D CT data, the axis of the femoral neck (FN) can be exactly obtained three-dimensionally. On the basis of FN axis, an FN cross-sectional image is obtained to calculate several parameters, such as BMD, bone mass, bone area, curvature, and cortical thickness. Bone biomechanical indices such as cross-sectional moment of inertia (CSMI), section modulus (SM), and buckling ratio (BR) also induced from these geometrical parameters

two-dimensional projection (anterior-posterior) of three-dimensional CT information with software to calculate the area bone density (mg/cm^2) in the femoral neck, intertrochanteric area, and shaft integral bone, as in the DXA method.

CTXA provides geometrical parameters such as bone area, curvature, perimeter, cortical thickness and so on.

2.2.3 Predicting Osteoporosis Fracture Using the QCT

The main purpose of a QCT study is to predict the fracture risk in patients with osteoporosis, and several studies have shown that the QCT-based BMD is a more sensitive method to predict fracture risk [9, 10].

Using geometrical parameters, biomechanical properties are derived such as cross-sectional moment of inertia (CSMI), section modulus (SM), and buckling ratio (BR).

2.2.4 Assessment of the Trabecular Microarchitecture with MDCT

To visualize the trabecular microstructure, the rotation speed of the X-ray tube in MDCT is less than 300 ms, with a spatial resolution of less than a millimeter. With a small field of view of 10 cm, the in-plane and through-plane spatial resolutions can be close to 200–500 μm, which is larger, but close to the trabecular size (100–150 μm).

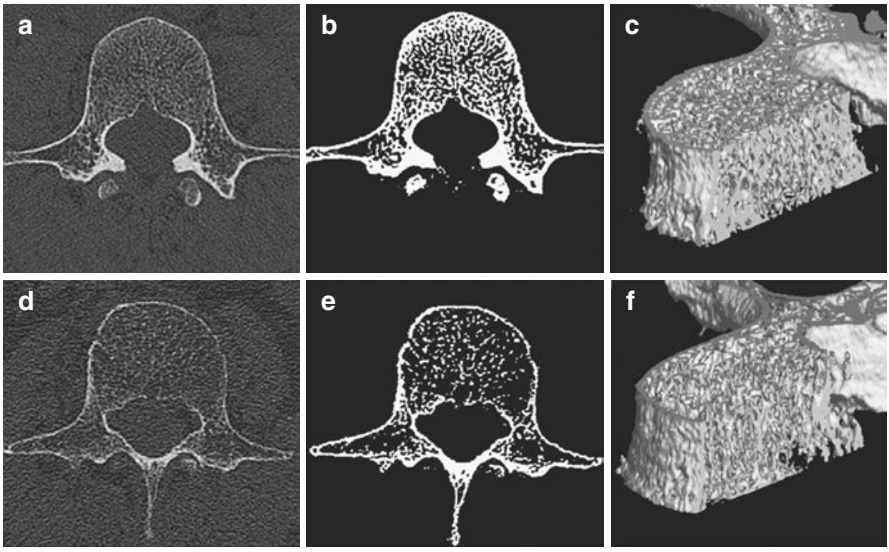

Fig. 10 Trabecular microstructure using multi-detector row CT (MDCT). Representative 2D and 3D MDCT images of the third lumbar spine. (**a** and **b**) 2D and (**e** and **f**) 3D MDCT images of the third lumbar spine were obtained from (**a** and **e**) a 62-year-old woman without vertebral fracture and (**b** and **f**) a woman of the same age with a vertebral fracture in her thoracic spine. (**c** and **d**) Binarized images are also shown [11]

BV/TV, Tb.N, Tb.Th, and Tb.Sp, connectivity, and the structure model index (SMI) are calculated two-dimensionally using plate model assumptions or direct three-dimensional measures (Fig. 10) [11]. Due to the lower spatial resolution than pQCT or μCT, the partial volume effect is relatively large. The advantage of the MDCT technique is that both the central and peripheral regions of the skeleton can be assessed, such as the spine, proximal femur, and extremities [11, 12]. Studies have shown that the BV/TV and SMI measured from the lumbar spine by MDCT provided a better result for predicting fracture risk [11] and in therapeutic evaluation than BMD measurement with DXA or QCT. Currently, bone microarchitecture assessment of the lumbar spine using MDCT is still limited due to radiation dose concerns.

2.2.5 Assessment of Bone Mechanical Properties

BMD and microarchitecture-based mechanical assessment (finite-element analysis, FEA) can effectively estimate the bone strength or stiffness, which is directly related to fragility fracture.

FEA is a well-established computational tool for complex engineering problems, and it has also been a valuable tool for investigating biological problems, such as bone mechanical testing. It includes the use of mesh generation techniques that can divide a complex problem into finite elements. During the past two decades, its

usage has been growing rapidly following the revolution of the MDCT technique and the universally increased awareness of osteoporosis [13].

QCT-based FEA integrates bone density or microarchitecture (BV/TV, plate-like or rod-like trabecula) data [14] and the geometric distribution. The two- or three-dimensional finite element model map contains the pixel or voxel data of BMD or microarchitecture and the combined geometric behaviors that are related to the orientation of loading force. Therefore, the FEA provides an assessment of bone strength or stiffness.

References

1. Genant HK, Wu CY, van Kuijk C, et al. Vertebral fracture assessment using a semiquantitative technique. J Bone Miner Res. 1993;8:1137–48.
2. Wu CY, Li J, Jergas M, et al. Diagnosing incident vertebral fractures: a comparison between quantitative morphometry and a standardized visual (semiquantitative) approach. In: Genant HK, Jergas M, van Kuijk C, editors. Vertebral fracture in osteoporosis. Radiology Research and Education Foundation; 1995. p. 281–91.
3. Delmas PD, Genant HK, Crans GG, Stock JL, Wong M, Siris E, Adachi JD. 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.
4. Leidig-Bruckneer G, Genant HK, Minne HW, Storm T, Thamsberg G, Bruckner T, Bauer P, Schilling T, Sorenson OH, Siegler R. Comparison of semiquantitative and quantitative method for assessing vertebral fractures in osteoporosis. Osteop Int. 1994;3:154–61.
5. Genant HK, Jergas M, Palermo L, Nevitt M, Valentin RS, Black D, Cummings SR. Comparison of semiquantitative visual and quantitative morphometric assessment of prevalent and incident vertebral fractures in osteoporosis the study of osteoporotic fractures research group. J Bone Miner Res. 1996;11:984–96.
6. World health organization assessment of the fracture risk and its application to screening for postmenopausal osteoporosis. Report no WHO technical report series 843 GW; 1994. p. 1–129.
7. CE Cann, HK Genant: precise measurement of vertebral mineral content using computed tomography. J Comput Assist Tomogr 4: 493–500, 1980.
8. Khoo BC, Brown K, Cann C, Zhu K, Henzell S, Low V, et al. Comparison of QCT-derived and DXA-derived areal bone mineral density and T scores. Osteoporos Int. 2009;20:1539–45.
9. Engelke K, Libanati C, Liu Y, Wang H, Austin M, Fuerst T, et al. Quantitative computed tomography (QCT) of the forearm using general purpose spiral whole-body CT scanners: accuracy, precision and comparison with dual-energy X-ray absorptiometry (DXA). Bone. 2009;45:110–8.
10. Lang TF, Augat P, Lane NE, Genant HK. Trochanteric hip fracture: strong association with spinal trabecular bone mineral density measured with quantitative CT. Radiology. 1998;209:525–30.
11. Ito M, Ikeda K, Nishiguchi M, Shindo H, Uetani M, Hosoi T, et al. Multi-detector row CT imaging of vertebral microstructure for evaluation of fracture risk. J Bone Miner Res. 2005;20:1828–36.
12. Issever AS, Link TM, Kentenich M, Rogalla P, Schwieger K, Huber MB, et al. Trabecular bone structure analysis in the osteoporotic spine using a clinical in vivo setup for 64-slice MDCT imaging: comparison to microCT imaging and microFE modeling. J Bone Miner Res. 2009;24:1628–37.

13. Liebl H, Garcia EG, Holzner F, Noel PB, Burgkart R, Rummeny EJ, et al. In-vivo assessment of femoral bone strength using finite element analysis (FEA) based on routine MDCT imaging: a preliminary study on patients with vertebral fractures. PLoS One. 2015;10:e0116907.
14. Keaveny TM, Hoffmann PF, Singh M, Palermo L, Bilezikian JP, Greenspan SL, et al. Femoral bone strength and its relation to cortical and trabecular changes after treatment with PTH, alendronate, and their combination as assessed by finite element analysis of quantitative CT scans. J Bone Miner Res. 2008;23:1974–82.