Special Report



Women's Health

# Technologies for assessment of bone reflecting bone strength and bone mineral density in elderly women: an update

Reduced bone mineral density is a strong risk factor for fracture. The WHO's definition of osteoporosis is based on bone mineral density measurements assessed by dual x-ray absorptiometry. Several on other techniques than dual x-ray absorptiometry have been developed for quantitative assessment of bone, for example, quantitative ultrasound and digital x-ray radiogrammetry. Some of these techniques may also capture other bone properties than bone mass that contribute to bone strength, for example, bone porosity and microarchitecture. In this article we give an update on technologies which are available for evaluation primarily of bone mass and bone density, but also describe methods which currently are validated or are under development for quantitative assessment of other bone properties.

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Alvilde Dhainaut*[,1,2], Mari Hoff[2,3], Unni Syversen[4,5] & Glenn Haugeberg[1,6]

[1]Department of Neuroscience (INM) Norwegian University of Science & Technology (NTNU), Trondheim, Norway

[2]Department of Public Health & General Practice (ISM), Norwegian University of Science & Technology, Trondheim Norway

[3]Department of Rheumatology, St. Olav's Hospital, Trondheim, Norway

[4]Department of Cancer Research & Molecular Medicine (IKM), NTNU, Trondheim, Norway

[5]Department of Endocrinology, St Olav's Hospital, Norway

[6]Department of Rheumatology, Hospital of Southern Norway, Kristiansand S, Norway

*Author for correspondence:
Tel.: +47 7257 5888
alvilde.dhainaut@ntnu.no

Bone is a mineralized connective tissue, and is comprised of 80% cortical (compact) and 20% trabecular (cancellous) bone. The load-bearing capacity of bone depends on the amount of bone (i.e., mass), the size, the spatial distribution of the bone mass (i.e., geometry and microarchitecture) and the intrinsic properties of the materials that form the bone [1,2]. Osteoporosis is a systemic skeletal disease characterized by low bone mass and microarchitectural deterioration of bone tissue with a consequent increase in bone fragility and susceptibility to fracture [3]. The consequences of fragility fracture are reduced quality of life and increased disability and mortality [4]. Fragility fractures in elderly individuals also cause substantial monetary costs and demand large health resources [5]. Due to the aging of the population worldwide, the number of fragility fractures related to osteoporosis will rise [6]. Thus, osteoporosis is a severe global health problem and a disease which needs to be diagnosed and treated properly. Low bone mass is part of the definition of osteoporosis, and assessment of bone mineral density (BMD) reflecting bone mass is the cornerstone in the diagnosis, risk prediction and monitoring of treatment with antiosteoporotic drugs [5]. BMD has been shown to account for up to 60–90% of the variation in bone strength [7,8].

## From BMD to assessment of fracture risk

The WHO operational definition of osteoporosis is based on BMD measurement at the hip (femoral neck and total hip) and/or lumbar spine by dual x-ray absorptiometry (DXA). The definition of normal BMD, osteopenia and osteoporosis is based on DXA BMD cut-off values where the measured BMD values are compared with reference BMD values from young adult females and expressed in standard deviations (SD; T-score). The T-score cut-off for osteoporosis is a BMD value ≤-2.5 SD below the young female adult mean [3]. The operational definition has been refined by WHO

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with the femoral neck as the proposed standard measurement site, and the use of an international reference standard from young women (NHANES III study) for the calculation of the T-score for both men and women [5,9].

It is controversial to use devices other than DXA for assessment of osteoporosis. The National Osteoporosis Society (NOS) has in their 2011 practical guide "Peripheral x-ray absorptiometry in the management of osteoporosis" [10] emphasized that use of axial DXA is preferable, but acknowledges that the use of less expensive and more convenient methods for evaluation of BMD are appealing. NOS recommends that in centers using peripheral BMD measurements, a triage approach with two thresholds should be applied. The upper thresholds are set to identify those who with 90% certainty would fulfill the WHO criteria for osteoporosis, while the lower threshold have 90% certainly for a normal BMD [10]. Other guidelines such as those from the International Society for Clinical Densitometry (ISCD), National Osteoporosis Foundation (NOF) and American College of Rheumatology (ACR) also make a distinction between diagnostic classification and the use of BMD for fracture risk assessment.

For fracture risk assessment, there is an agreement that many techniques can be applied [11–14]. The guidelines point out that BMD from different devices cannot be directly compared, and T-scores from measurements other than DXA cannot be used for the WHO diagnostic classification. According to these guidelines, DXA is also preferred for treatment decisions. However, if central DXA cannot be performed, assessment of fracture risk can be done on the basis of peripheral measurements and/or clinical risk factors, and treatment can be initiated [13,15].

Several other methods than DXA have been developed to assess BMD, and an increase in fracture risk with declining BMD has been shown using various techniques both at central and peripheral sites [16]. Even though BMD influences fracture risk, many women with fracture do not have low BMD and many women with low BMD do not fracture [17,18].

Several risk prediction algorithms based on fracture risk factors have been developed to estimate future fracture probability [19]. Among these is the FRAX® developed by the WHO, based on individual models that integrate the risk associated with clinical risk factors as well as BMD at the femoral neck. FRAX is designed to estimate a 10-year probability of hip and major osteoporotic fracture among men and women, aged 40–90 years [20]. FRAX can be used with or without BMD. Models for fracture risk prediction have several limitations. For example, in the FRAX model, neither risk of falling nor previous falls are included. Other limitations are that FRAX does not consider the dose–response relationship for number of fractures, alcohol use, smoking, use of glucocorticoids, or low BMD at other sites [21]. On the other hand, it is not certain that more complicated models including more risk factors would give better fracture prediction. In a study by Ensrud and colleagues, including women over 65 years, simple models based on age and BMD alone, or age and fracture history alone predicted 10 year risk of hip, major osteoporotic and clinical fracture, just as good as the more complex FRAX model [22]. In a systematic review including available risk assessment tools for fractures published in 2013 by Rubin *et al.*, complex tools did not perform better than more simple tools [23]. Type II diabetes mellitus is an example of a condition where DXA-BMD and FRAX underestimate the fracture risk, and where other features of bone quality might enhance the fracture prediction [24].

During recent years there has been an increased interest in studying other bone features contributing to bone strength than BMD, for example, finding methods to not only evaluate bone quantity but also bone quality such as bone geometry, microarchitecture and material properties.

In this article we give an update of technologies for assessment of BMD and bone quality.

## Technologies for the assessment of BMD

### Dual-energy x-ray absorptiometry

The DXA is the gold standard for diagnosis of osteoporosis according to WHO, and is also the method of choice for measurement of BMD in clinical trials [25–27] and observational studies [28,29]. Further, DXA-BMD at the femoral neck is used in the fracture risk assessment tool FRAX [30] which is implemented in several guidelines [5,13,31].

DXA measures the attenuation of x-ray beams with two different energies during radiation transmission. Bone mineral content (BMC) of a region is obtained, and DXA-BMD corresponds to the ratio between BMC and the scanned area. Since it is a 2D measure, larger bones may have higher BMD than smaller bones because of size. Further, DXA does not distinguish between cortical or trabecular bone. DXA can be applied both to measure central (e.g., spine and hip) and peripheral parts of the skeleton (e.g., heel and distal radius). DXA devices with additional laser, for example, DXL techniques are also available [32]. Development of new softwares has also made it possible to assess bone geometry, including hip structural analysis (HSA) and vertebral assessment (VFA) with DXA [2,33–35]. Software for evaluation of bone microarchitecture in the spine is also available. This is based on the analy-

sis of the gray level variation present in the x-ray projected image, which reflects trabecular architecture and is referred to as trabecular bone score (TBS) [36].

### Single energy x-ray absorptiometry

Single x-ray absorptiometry (SXA) applies the same principle as DXA, but only one energy beam is used for BMD assessment at the forearm and heel [35]. The tool, which is feasible to use, has been applied in population studies and thus useful in longitudinal studies of old cohort, but has been less used in clinical care [37].

### Quantitative computed tomography

Similar to DXA, quantitative computed tomography (QCT) applies a photon absorptiometric technique, but in contrast, the x-ray source and the detector rotate around the subject, and thus permit generation of 3D images. A bone mineral phantom allows calibration of data and provides a volumetric measure of BMD independent of bone size. QCT can differentiate between cortical and trabecular bone and can be used at both central and peripheral skeletal sites [2,33–35]. There is, however, a lack of data validating the QCT method for fracture prediction although some parameters has been shown to be predictive for fracture [38,39]. A QCT device is also included in the list of devices that may be applied for BMD measurements in FRAX.

High resolution peripheral QCT (HRpQCT) is a refinement of QCT. This method has a higher spatial resolution and can be used for assessment of smaller areas at distal skeletal sites. The method can evaluate microarchitecture such as trabecular number, thickness and separation, cortical thickness and porosity [2,33–35].

### Quantitative ultrasound

Quantitative ultrasound (QUS) measures velocity (speed of sound) and frequency-dependent attenuation (broadband ultrasound attenuation) and not BMD *per se*. The speed through bone and how fast energy is lost, depend both on BMD and microarchitectural qualities such as porosity and trabecular connectivity. Thus, this method gives a quantitative measure of bone density, however, not directly comparable to other densitometric tools. QUS is used for measurement at peripheral sites, for example, calcaneus, radius, metacarpal bones and tibia. Several of the developed devices are relatively small and may thus also be portable [2,33–35,40]. QUS measurements have been shown to be predictive for fracture at the same level as measurements by DXA [41,42].

QUS methods for spine are also developed [43], and there are ongoing studies using ultrasound for quantitative measurements of cortical bone at the femoral neck [44].

### Radiographic absorptiometry

This method measures BMD in the phalanges by comparing the skeleton to a known reference wedge on radiographs giving BMD in arbitrary units [35]. Radiographic absorptiometry has been shown to be predictive of fractures [45]. An advantage is that portable devices are available [46]. The radiographic absorptiometry device may also be installed on regular x-ray equipment [47].

### Conventional radiographs

Plain radiographs are widely available and can give information on bone structure and other aspect of structure and/or bone geometry including textural analysis, for example, at the hip but also at other sites [48,49].

Digital x-ray radiogrammetry (DXR) is a computer version of the traditional technique of radiogrammetry [50] and estimates cortical BMD from defined regions of interest in the second, third and fourth metacarpal bone in the hand. Based on geometrical equations, BMD is calculated from measurements of cortical thickness and bone width and further corrected for porosity and scaled to DXA. Porosity is derived from the area percentage of local intensity minima (hole) in the cortical part relative to the entire cortical area. DXR can be analyzed both from conventional x-rays and from digitized x-rays [51,52]. DXR-BMD has been shown to be predictive of fracture [53]. The potential for measuring porosity might be of importance in fracture risk assessment [54].

Other techniques using plain radiographs are mandible osteoporosis radiography measuring trabecular pattern and mandibular cortical width [55].

### MRI

MRI uses a magnetic field and a series of radiofrequency pulses to generate a nonionizing 3D image based on hydrogen in water. Although it can be used for BMD measurements [56], it is mainly used for structural analyses. As there is low water content in bone, MRI gives indirect images of bone microarchitecture via measurements of the marrow and other soft tissues. High resolution MRI applies clinical magnetic resonance scanners combined with specially designed coils to improve resolution, and may be performed at distal sites [2,33–34,57].

## Conclusion & future perspective

Features associated with bone quality including macro- and microarchitecture of both cortical and trabecular bone, and biochemical composition of bone tissue have up to now mostly been studied in animal studies or *ex vivo*. Techniques such as HR-QCT and

Table 1. Bone assessment techniques *in vivo*.

| Techniques | Site | Measurements | CV% | Pros | Cons | Ref. |
|---|---|---|---|---|---|---|
| Dual-energy x-ray absorptiometry DXA | Spine, hip, forearm | aBMD/HSA/VFA/TBS | 1–3/2–10†/2/2 | Many validation studies, diagnostics used in WHO definition (aBMD)<br>Can measure several sites and several applications | Areal measurements and not volumetric<br>Do not distinguish cortical and trabecular bone | [79,82–84] |
| Radiographic absorptiometry | Phalanx, metacarpals | BMD | 1–2 | Portable devices | No central measure possible | [82] |
| Quantitative computed tomography/high resolution QCT | Spine, hip, forearm | vBMD/microarchitecture | 2–4/1–8† | Separate cortical and trabecular bone<br>Structure analysis<br>Volume BMD can be more correct for very small or very large or obese | Higher radiation than DXA<br>Less validated | [74] |
| Digital x-ray radiogrammetry | Metacarpals | ‡DXRBMD/porosity | 0.3–0.5/3§ | Use standard x-ray<br>Low radiation<br>High precision<br>Can be used for historical x-rays | No central measure possible | [54,85] |
| Quantitative ultrasound | Calcaneus | BUA, SOS | 1.5–4 | Portable devices<br>No radiation | | [82] |
| MRI | Spine, hip, forearm | Microarchitecture | 2–7† | Microarchitecture<br>Volume and structure<br>No radiation | Higher costs and low availability<br>Poor precision | [74] |
| Positron emission tomography | Spine, hip | Bone turnover | 9–14 | Bone turnover | Higher radiation<br>Higher costs and low availability | [86] |
| Microindentation | Tibia | Hardness/strength | 8–15 | Direct measure of a bone property | Invasive<br>Less validated<br>Poor precision | [73] |

†Depending what parameter and/or site.
‡BMD estimated from other parameters.
§Precision measured *ex- vivo*.
aBMD: Areal bone mineral density; BMD: Bone mineral density; BUA: Broadband ultrasound attenuation; CV: Coefficient of variation; DXA: Dual x-ray absorptiometry; DXR: Digital x-ray radiogrammetry; HSA: Hip structural analyses; QCT: Quantitative computed tomography; SOS: Speed of sound; TBS: Trabecular bone score; vBMD: Volume bone mineral density; VFA: Vertebral fracture assessment.

HR-MRI, have enabled the assessment of the quality of bone also *in vivo*. These techniques provide information on microarchitecture. When combined with advanced image processing and computational approaches such as finite element analysis modeling techniques, they can be used for prediction of bone structural properties [58–61]. Also for the more traditional techniques DXA, US and DXR, new modes for use and evaluation of bone quality parameters are developed.

Cortical porosity is one of the bone features that have been studied in the last few years. Haversian channels and resorption cavities in cortical bone give rise to a porous bone tissue with pore diameters ranging from a few up to several hundred micrometers [62]. In an *ex vivo* study with micro CT, Ural *et al*. showed that intracortical porosity is a significant contributor to the fracture resistance of the bone [63]. Granke *et al*. observed that change in porosity is the major determinant of the variation of cortical bone elasticity in aged women [64]. Furthermore, Zebaze *et al*. explored porosity in cortical bone, and found large pores, resulting from intracortical remodeling, thinning the cortex from inside and leaving remnants that looked similar to trabecular bone. Cortical bone loss due to intracortical porosity is poorly captured by DXA [65]. *In vivo* studies have shown that postmenopausal women with osteopenia have higher cortical

porosity at distal radius than women with normal BMD [66]. Age-related differences in cortical porosity, as detected by HR-pQCT, are more pronounced than differences in standard cortical metrics [67]. Cortical porosity is also associated with distal radius fracture [54,68].

There are emerging techniques for examining tissue composition such as infrared and Raman spectroscopy, providing information on the quality of the bone matrix. So far, these measurements have to be performed in bone biopsies [69,70].

Nuclear MRI (NMRI) or solid-state MRI can also be used to provide information on tissue composition. *In vivo*, the method is limited to analyses of finger, hand and wrist [10,14–15].

Bone turnover has usually been assessed by measuring markers in serum [71]. Recently imaging techniques for exploring bone turnover have been developed, such as dynamic fluorine-18 labeled sodium fluoride positron emission tomography ($^{18}$F-NaF PET) that allows the quantitative assessment of regional bone formation by measuring the plasma clearance of fluoride to bone at any site in the skeleton [72].

Another measurement of bone strength shown to discriminate patients with fragility fracture is microindentation [73]. There is a relationship between resistance to indentation and mechanical properties influenced by both elastic and plastic behavior of bone tissue [74,75]. Methods for possible intraoperative information about bone strength are also developed such as transpedicular measurement of the peak breakaway torque [76].

Ultrasound has been applied for quantitative measurements, but new *in vivo* applicable methods permit measurements of fracture-relevant properties, for example, cortical thickness and stiffness at the distal radius and the proximal femur [77].

DXA, the cornerstone in BMD measurements, can also be used for assessment of other parameters than BMD, for example, HSA, VFA or lumbar spine texture analysis using TBS that can enhance fracture prediction [78,79]. A more proactive vertebral assessment is also advocated as in the NOF guidelines [13]. Vertebral assessment can be done on plain x-ray or from DXA [80,81].

There are major differences in precision for the various tools as listed in Table 1. What method and site to choose depends on whether the purpose is for diagnostic use, for fracture risk assessment or for follow-up assessment of bone changes.

The advances in bone assessment technologies provide opportunities to reveal other bone properties contributing to bone strength than BMD. They can address the 'microarchitectural deterioration' aspect of the definition of osteoporosis as "…a systemic skeletal disease characterized by low bone mass and microarchitectural deterioration of bone tissue with a consequent increase in bone fragility and susceptibility to fracture" [3]. Moving from bone quantity to bone quality may, in the future, improve fracture prediction. This is of major importance to better identify patients at high risk of fracture and to reduce the burden of osteoporotic fractures in the future.

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### Executive summary

- Bone mineral density measured by dual x-ray absorptiometry (DXA) is the cornerstone in diagnostics of osteoporosis according to the WHO criteria.
- FRAX or other fracture risk assessment tools can be helpful with or without bone mineral density for fracture prediction.
- Other densitometric techniques than DXA can be used for fracture prediction and/or prescreening.
- Bone quality features can improve identification of individuals at high risk. Methods for investigating bone quality *in vivo* are being developed:
  - DXA: geometry, trabecular bone score;
  - HRQCT: microarchitecture, cortical bone, including porosity;
  - MRI: microarchitecture;
  - Quantitative ultrasound: cortical thickness, stiffness of bone;
  - Digital x-ray radiogrammetry: cortical porosity;
  - Microindentation: hardness of bone.

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