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ASSESSMENT OF BONE HEALTH

Clinical Vignettes: Using Non-BMD Measurements in Clinical Practice

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Abstract Dual-energy X-ray absorptiometry (DXA) is a well-established clinical tool for measuring bone mineral density (BMD) in the assessment of patients at risk of fracture. DXA is commonly used to diagnose osteoporosis, assess fracture risk, and assess the skeletal effects of treatment. Non-BMD DXA measurements, such as vertebral fracture assessment, hip access length, and trabecular score, have clinical applications that can guide patient treatment decisions. Quantitative computed tomography (QCT) measures three-dimensional volumetric BMD that is correlated with fracture risk. QCT measurements of the hip can also be used to generate a two-dimensional DXA-equivalent areal BMD and T-score that can be used for diagnosis of osteoporosis and the assessment of fracture risk in the FRAX algorithm. Opportunistic measurements of BMD obtained with CT scans evaluating non-skeletal conditions have potential clinical utility in identifying patients at high risk of fracture. This is a collection of clinical vignettes that illustrate potential applications of non-BMD DXA measurements and CT scanning in the management of patients at risk of fracture.

Keywords Osteoporosis · Treatment · Hip geometry · DXA · Trabecular bone score

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Introduction

Measurement of bone mineral density (BMD) by dual-energy X-ray absorptiometry (DXA) is used to predict fracture risk [1], diagnose osteoporosis [2], and monitor changes in BMD over time [3]. Other applications of DXA include BMD input into fracture risk algorithms [4–6], vertebral fracture assessment (VFA) [7], analysis of body composition [8], measurement of hip structural parameters [9], and derivation of trabecular bone score (TBS) [10]. DXA provides a two-dimensional (2D) projection of bone that generates a value for areal BMD in g/cm^2 and T-scores for postmenopausal women and men age 50 years and older. Quantitative computed tomography (QCT) is a radiographic technology that provides a three-dimensional (3D) view with measurement of volumetric BMD (vBMD) in mg/cm^3 at the spine and hip, with the capability of 2D projections of the femoral neck and total hip that can be used to calculate T-scores that are equivalent to DXA T-scores [11]. The World Health Organization (WHO) diagnostic criteria for osteoporosis can be used with lumbar spine, femoral neck, total hip, and 33 % (one-third) radius DXA T-scores and with femoral neck and total hip DXA-equivalent T-scores generated from 2D QCT projections [11]. Peripheral DXA (pDXA) devices use DXA technology to measure BMD at peripheral skeletal sites (e.g., forearm, calcaneus). Peripheral QCT (pQCT) devices use QCT technology to measure vBMD at peripheral sites, such as the forearm or tibia. QCT provides separate vBMD measurements for cortical and trabecular bone compartments, which in some instances can be used for fracture prediction. QCT measurements can be used for making treatment decisions and monitoring vBMD changes over time, although DXA is preferred because of lower radiation exposure, lower cost, and greater availability. Finite

element analysis (FEA) of the spine and hip is a QCT-based methodology for estimating bone strength and predicting fracture risk. Although FEA is primarily a research tool with very limited availability in clinical practice, it has potential clinical applications.

At the 2015 International Society for Clinical Densitometry (ISCD) Position Development Conference, held in Chicago, Illinois, USA, on February 26–18, 2015, the medical evidence for applying advanced non-BMD measures of DXA and QCT to clinical practice was reviewed and evaluated by a panel of experts in the assessment of skeletal health. The results were presented in a series of six publications that identified new ISCD Official Positions, with the rationale for establishing each of them [12–17]. These publications were accompanied by an executive summary that included all ISCD Official Positions [11]. This is a collection of clinical vignettes illustrating potential applications of selected non-BMD DXA and QCT measurements to patient care.

Vertebral Fracture Assessment

A 69-year-old Caucasian woman with no known fracture has a screening bone density test by DXA according to USA guidelines from the National Osteoporosis Foundation (NOF) [18]. The lowest relevant T-score is −2.1 at the left femoral neck, consistent with a diagnostic classification of low bone mass (osteopenia). She has no FRAX-related clinical risk factors for fracture. The FRAX algorithm shows a 10-year probability of major osteoporotic fracture (MOF) of 11 % and a 10-year probability of hip fracture (HF) of 2.3 %. These values are below the NOF treatment thresholds of ≥20 % for MOF and ≥3 % for HF [18]. However, because of historical height loss of 1.5 inches, VFA is performed. This shows a prevalent grade 3 vertebral wedge fracture at the level of T12 (Fig. 1) using the Genant semiquantitative method for diagnosing vertebral fractures [19], as recommended by the ISCD [20]. There is no history of spine trauma. According to the NOF guidelines, treatment to reduce fracture risk is now recommended. A repeat FRAX calculation with inclusion of previous fracture as a clinical risk factor raises MOF risk to 17 % and HF risk to 3.5 %.

Comments. Imaging of the spine with VFA in this patient revealed a previously unrecognized vertebral fracture. This resulted in a change in diagnostic classification from osteopenia to osteoporosis, an increase in the FRAX estimation of fracture risk, and a recommendation to treat with a pharmacological agent rather than non-pharmacological therapy. Although standard spine radiographs could have also provided the diagnosis of vertebral fracture, VFA is less expensive, exposes the patient to a lower dose of radiation, and is usually more convenient, since it is a "point of service" procedure can be done in conjunction with BMD testing by DXA [7]. VFA for the diagnosis of grades 2 and 3 vertebral fractures compares favorably with standard spine radiographs for accuracy, reliability, and inter-observer agreement [7]. Image resolution is better with conventional radiography than VFA, although there is less parallax effect with VFA that may sometimes allow for superior viewing of vertebral endplates. Performance of VFA requires a fan-beam DXA system with appropriate software using either single-energy or dual-energy mode placed in a lateral decubitus or supine lateral position with a rotary C-arm, depending on the manufacturer and model of the DXA system. The spine image can be manipulated to optimize magnification, contrast, and brightness in order to enhance visualization of vertebral deformities. Point markers can be manually or automatically placed at the anterior, middle, and posterior margins of the vertebral

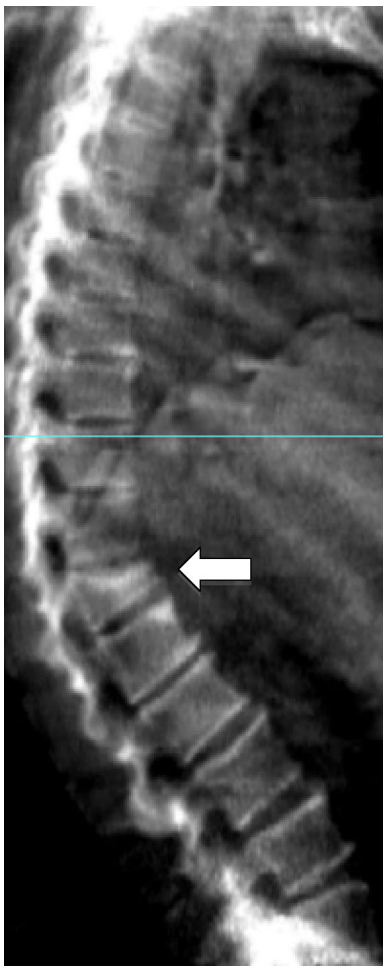

Fig. 1 Vertebral fracture assessment by dual-energy X-ray absorptiometry showing a grade 3 vertebral fracture at the level of T12. Identification of a previously unrecognized vertebral fracture may change diagnostic classification, assessment of fracture risk, and treatment decisions [7]

endplates as a tool for measuring vertebral body heights and ratios, if desired.

Spine images can be viewed on a computer monitor or as a paper printout. The ISCD recommends VFA or lateral spine imaging with standard radiography when the T-score is <-1.0 and one or more of the following is present: women age $\geq$70 years or men age $\geq$80 years, historical height loss >4 cm (1.5 inches), self-reported but undocumented prior vertebral fracture, glucocorticoid therapy equivalent to $\geq$5 mg of prednisone or equivalent per day for $\geq$3 months [11].

Hip Access Length

A 64-year-old Caucasian woman has a DXA T-score of −1.4 at the femoral neck. The FRAX 10-year probability of HF is 2.5 %, below the NOF threshold for pharmacological intervention to reduce fracture risk. When the HAL measurement of 114 mm was taken into consideration, the 10-year probability of hip fracture was adjusted upward by 33 % (assuming an increase in relative HF risk of 4.7 % for every 1-mm increase in HAL above reference range mean, estimated to be 107 mm). This resulted in a revised HF probability of about 3.3 %, well above the NOF threshold for initiating pharmacological therapy. Based on this information, treatment is now recommended.

Comments. HAL is conventionally defined as the distance from the base of the greater trochanter to the inner pelvic brim. It can be measured manually or with commercially available DXA software (Hip Structural Analysis (HSA) from Hologic, Bedford, MA, USA; and Advanced Hip Assessment (AHA) from General Electric (GE Lunar, Madison, WI, USA). HAL varies according to ethnicity and gender, with a longer HAL associated with greater risk of hip fracture, even when adjusted for age, height, weight, and femoral neck BMD [16]. Asians typically have a shorter HAL than other ethnicities, and men typically have a longer HAL than women [16]. A recent review of the studies evaluating the correlation of HAL and hip fractures in multiple populations found that HAL predicts hip fractures in postmenopausal women, but not in men [16]. A subsequent publication analyzed a large database of patients (4738 men and 50,420 women) in Manitoba, Canada; it was concluded that greater HAL measured by DXA is associated with increased incident HF risk in both men and women, and this risk is independent of BMD and FRAX probability [21]. A bilinear adjustment applicable to both men and women showed a relative increase in HF probability of 4.7 % for every mm that HAL is above the sex-specific average and a relative decrease in HF probability of 3.8 % for every mm that HAL is below the sex-specific average. In the clinical vignette presented here, the reference range mean of 107 mm and adjustment of 4.7 % for each mm increase in HAL were taken from the Canadian study. The use of HAL in aiding clinical practice decisions remains somewhat aspirational, since it requires that an applicable reference range and mean HAL are known and that therapeutic interventions guided by HAL are effective in reducing fracture risk. HAL cannot be used to monitor therapy, since no treatment is known to change HAL. Independent validation with larger numbers of men and women of diverse ethnicities is needed before adjustments in fracture risk estimates can be widely applied.

Trabecular Bone Score

A 72-year-old Caucasian obese woman with long-standing type 2 diabetes mellitus has a femoral neck T-score of −1.8. She sustained an ankle fracture from a twisting injury at age 68. FRAX with input of femoral neck BMD and previous fracture show MOF risk 17 % and HF risk 2.9 %, below the NOF threshold for starting treatment. When the lumbar spine TBS of .935 is added to the FRAX calculation, the estimated MOF is 24 % and HF risk is 4.7 %. She now meets the NOF guideline for starting drug treatment to reduce fracture risk.

Comments. TBS is a gray-level textural index derived from the lumbar spine DXA image with late generation DXA systems of GE Lunar (Madison, WI, USA) and Hologic (Waltham, MA, USA) using commercially available dedicated software (TBS iNsight, Medimaps, Plan-les-Ouates, Switzerland). The TBS result is a unitless value for each lumbar vertebra and for L1-L4. In ex vivo studies, TBS has been correlated with measures of trabecular microarchitecture that include connectivity density, trabecular number, and trabecular separation [15]. When the amplitude of pixel-value variations is measured from the 2D lumbar spine image, a dense trabecular structure produces a high TBS value, while a degraded trabecular structure produces a low TBS value. Abnormal TBS has been reported to have an association with fracture risk that is at least partially independent of BMD by DXA and clinical risk factors [15]. The potential clinical applications of TBS were considered at the 2015 ISCD Position Development Conference. Following a review of the medical evidence by a panel of experts, it was concluded that TBS is associated with vertebral fracture, HF, and MOF risk in postmenopausal women and with HF and MOF risk in men greater than age 50 years [15]. It was determined that TBS can be used with FRAX and BMD to adjust the estimation of fracture probability. TBS is now incorporated into the FRAX algorithm for use in clinical practice. TBS should not be used alone to make treatment recommendations and is not useful for monitoring the skeletal effects of bisphosphonate therapy in postmenopausal women with osteoporosis.

Type 2 diabetes mellitus has been identified as a special condition for which TBS is associated with MOF risk in postmenopausal women [15]. In a retrospective cohort study that included 29,407 women in a large clinical registry in Manitoba, Canada, 2356 (8.1 %) were diagnosed with diabetes. Over a mean follow-up time of 4.7 years, the incidence of at least one MOF was significantly higher in diabetics than in non-diabetics ($P < 0.001$), despite diabetics having higher BMD at all measured skeletal sites than non-diabetics [22]. However, lumbar spine TBS in diabetics was lower than in non-diabetics, with TBS being a BMD-independent predictor of fracture risk that captured a larger proportion of diabetes-associated fractures than BMD alone.

Quantitative Computed Tomography for Diagnosis and Fracture Risk Assessment

An elderly man has multiple risk factors for fracture, including androgen deprivation therapy for prostate cancer, parental history of hip fracture, and cigarette smoking. The only DXA facility in his community recently closed. The local hospital has a CT scanner with software capable of QCT for measuring a DXA-equivalent T-score of the hip. This shows a T-score in the osteoporosis range, resulting in initiation of pharmacological therapy to reduce fracture risk.

Comments. Data derived from 3D QCT can be used to simulate a 2D DXA-like image using software such as QCTPro in CTXA (CT X-ray absorptiometry) mode (Mindways Inc., Austin, TX, USA) and VirtuOst (ON-Diagnostics, Berkeley, CA, USA). According to the ISCD Official Positions, "Femoral neck and total hip T-scores calculated from 2D projections of QCT data are equivalent to the corresponding DXA T-scores for diagnosis of osteoporosis in accordance with the WHO criteria [14]." 2D QCT is the only non-DXA technology that can be used with the WHO diagnostic criteria. CTXA DXA-equivalent T-scores and areal BMD of the femoral neck have recently been integrated into the FRAX algorithm for estimation of 10-year fracture probability. Although DXA-equivalent T-scores and BMD may be derived from QCT, this is not recommended for use in clinical practice unless DXA is not available due to greater radiation exposure and higher cost.

Opportunistic Quantitative Computed Tomography for Diagnosing Osteoporosis

A 69-year-old woman has a CT scan of the abdomen for evaluation of chronic abdominal pain. There were no findings to explain her pain. She had never had a DXA study, and there was no known fracture. The radiology facility has a special interest in osteoporosis and had known machine-specific cutoff values for low BMD at the hip and lumbar spine, with established scanner stability. Based on the values obtained with this scan, it was determined that the patient was at high risk of fracture and that further evaluation was indicated.

Comments. The 2015 ISCD Official Positions state that it is possible to screen patients with low BMD of the hip or spine with opportunistic CT scans, provided validated machine-specific cutoff values and scanner stability have been established [12]. This is problematic at most clinical CT facilities since this is most often not done. The effect of contrast material and CT acquisition parameters such as table height and X-ray tube voltage is unclear. Although the use of opportunistic assessment of fracture risk with CT scanning has the potential of great clinical utility, more data are needed before this can achieve established role in clinical practice.

Summary

Non-BMD measurements by DXA and CT were evaluated at the 2015 ISCD Position Development Conference. Some of these were found to have clinical utility for assessing fracture risk, diagnosing osteoporosis, and aiding treatment decisions. The clinical vignettes described here illustrate potential clinical applications of VFA, HAL, and TBS with DXA, as well as diagnosis of osteoporosis and estimation of fracture risk with CT. Each of the applications has important limitations. Interpreters of VFA must be trained to recognize vertebral fractures and distinguish them from non-fracture deformities. HAL measurements must be considered in the context of reference values, largely unavailable at this time, applicable to the patient. Although TBS is an approved technology for assessing fracture risk independently of BMD, it is not generally available at DXA facilities. CT scanning is more expensive than DXA and involves a much higher level of exposure to radiation. Opportunistic CT measurement of BMD and bone strength is possible only if validated machine-specific cutoff values and scanner stability have been established. Clinical use of non-BMD measurements with these technologies, under appropriate circumstances, may enhance the management of patients at risk of fracture.

Compliance with Ethical Standards

Conflict of interest The author has received institutional grant/research support from Amgen, Merck, and Eli Lilly; he has served on scientific advisory boards for Amgen, Merck, Eli Lilly, Radius Health, AgNovos Healthcare, Alexion, Shire, and AbbVie; he serves on the speakers' bureau for Shire.

Animal/Human Studies The author conducted no studies with animals or humans for the preparation of this manuscript.

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