

Review Article

Additional tools for the estimation of fracture risk using DXA method

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Abstract

As the world population grows, the life expectancy of the elderly will continue to grow. With the growing prevalence of various chronic diseases, the incidence of fragility fractures caused by osteoporosis is expected to further increase in the future. DXA is a simple, inexpensive and safe technique currently used for the diagnosis of osteoporosis, but numerous osteoporotic fractures also present in patients with osteopenia. Other techniques using the DXA technology also currently employed, such as the assessment of bone quality by analyzing bone microarchitecture with Trabecular Bone Score (TBS), or geometrical properties of the femur with Hip Structural Analysis (HSA) contribute to the prediction of fracture risk and bone strength, while Vertebral Fracture Assessment (VFA) serves in assessing prevalent vertebral fractures by replacing conventional X-ray.

Keywords: Dual-energy X-ray Absorptiometry, Hip Structural Analysis, Osteoporosis, Trabecular bone score, Vertebral Fracture Assessment

Introduction

Osteoporosis is mainly characterized by low bone mass as well as by bone microarchitectural deterioration, thus increasing the risk of fractures. Therefore, osteoporosis may cause a high fracture risk due to low intensity impact or loading forces. Patients at risk for fragility fractures may be identified by DXA and its T-score system.

DXA is a technique for measuring BMD, the major bone strength determinant, utilizing quantitative procedures. DXA scans produce bone mineral density reports in terms of [g/cm²]. The bone mineral density that is derived, is equal to BMC (bone mineral content in [g]) by ROI (region of interest) scanned in [cm²]. The results of DXA are reported as the SD (standard deviation) from mean BMD of a population of young healthy women, (T-score) and or an age-matched population (Z-score).

As defined by WHO (World Health Organization), based on the T-score of each person, osteoporosis is distinguished in the following four categories: normal bone density (T-score greater than or equal to -1.0 SD), osteopenia (T-score between -1.0 and -2.5 SD), osteoporosis (T-score less than or equal -2.5 SD) and established osteoporosis (T-score less than or equal -2.5 SD with one or more fragility fractures).

The World Health Organization's fracture risk assessment algorithm, which is well known as FRAX and

is the most widely used tool, takes into consideration a very important risk factor such as Femoral neck BMD by DXA, but also includes risk factors such as age, sex, previous fragility, smoking, alcohol consumption, use of corticosteroids or history of rheumatoid arthritis. This well-studied tool has various country specific versions and the algorithms may give a 10 year probability of major osteoporotic and hip fractures.

Nevertheless, many people who lie within the normal range for bone density or slightly below in the osteopenic ranges still suffer fragility fractures. This suggests that there may be other factors to consider when attempting to predict risk for fractures, such as geometry of the bone, micro-architectural changes, accumulated microfractures, rate of bone remodeling and others. Taking into account

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all of these factors, in addition to the aBMD, gives a much more comprehensive picture of the bone's overall health and therefore is a better risk indicator. Given this reality, efforts have been made in recent years to more accurately screen patients who may be at increased risk of fragility fractures by developing better assessment tools based on DXA, which is readily available. These adjunct techniques include VFA (vertebral fracture assessment), (TBS) trabecular bone score, as well as, DXA-derived hip structural analysis¹⁻⁶.

VFA

Vertebral fractures increase in direct correlation with age and have a direct impact on decreased quality of life and increased mortality and morbidity. It's therefore surprising that they remain frequently underdiagnosed, especially given their high value for in risk assessment for further fractures. Genant et al.⁷ describe the visual SQ (semi-quantitative) assessment of typical radiographs, which is the most widely accepted method used to identify VF: grade one for an anterior, mid or posterior decrease in vertebral height between 20 to 25%, grade two for a decrease between 25 and 40% and grade three for a higher than 40% decrease.

Vertebral fracture assessment is a technique used for thoracic and lumbar spine imaging by DXA. This method is mainly used for detecting vertebral fracture and is accomplished using images acquired by bone densitometers in the same period as bone mineral density measurements have been carried out.

Vertebral fracture assessment compared to conventional radiography

VFA technique has several advantages for the patient over conventional radiographs. It can aid in the VF diagnosis during the same visit as a BMD measurement. Additionally, the radiation exposure for the patient is minuscule (roughly 3-40 μ Sv) compared to the exposure associated with a conventional lateral thoracic and lumbar spine radiograph (over 600 μ Sv). The cost is potentially lower as well⁸.

Based on available data⁹, several clinical guidelines have already adopted VFA as their primary tool to assess prevalent vertebral fractures, and subsequently risk for fracture. In addition to the aforementioned advantages VFA has over conventional radiotherapy, it has been found that it comes with the trade-off of higher noise rates in the upper thoracic, between levels Th4 and Th6¹⁰. This problem also applies to X-ray, but to less extent¹¹. In addition, according to available data^{12,13}, the inferior resolution is directly related to reduced accuracy in the grade 1, mild fractures diagnosis.

Recently, vertebral fracture assessment technological developments may further improve performance compared to conventional radiography. Buehring et al¹⁴ found over 90 percent of all vertebrae to be evaluable on vertebral fracture assessment images using a newer Lunar-GE densitometer, compared to more than 75 percent on VFA images acquired on an older generation densitometer. According to a study¹⁵,

the most recently available Hologic vertebral fracture assessment technology also yields better images compared to elder Hologic densitometers. As a consequence, reported less than 2 percent of vertebrae not to be evaluable and for Genant SQ grade 2 or grade 3 prevalent vertebral fractures, vertebral fracture assessment was reported that has close to 100% specificity compared to radiographs and at least 93 percent sensitivity. This percentage may reach even higher values with the use of improved resolution technologies.

In addition, latest developments in image quality by new dual-energy X-ray absorptiometry devices may lead to higher accuracy of vertebral fracture assessment, further assisting mild VFs diagnosis^{16,17}. As indicated in¹⁷ vertebral fracture assessment by recent DXA devices showed high sensitivity and specificity in tremendous agreement with SQ assessment of spinal radiography, misclassifying only eleven vertebrae among more than 4500. Only three mild VF's identified by spinal radiography were not diagnosed by vertebral fracture assessment.

However, if there are two or more unavailable vertebrae below Th6, the presence of osteoarthritis¹¹, reduced visualization due to moderate to severe scoliosis¹⁸ or a need to confirm possible (grade 1) vertebrae fractures, additional confirmatory spine radiography should be considered¹⁹.

Indications for VFA

In 2019, the ISCD eased the indications in the diagnostic use of VFA using DXA spine images as a prospective alternative to typical radiography, in order to detect vertebral fracture in the screening of people with risk of osteoporosis and in the follow-up of osteoporotic patients undertaking treatment.

Densitometric vertebral fracture assessment is specified when T-score is lower than -1.0 and when one or more of the above exists²⁰:

- Age of Women higher or equal to 70 years or men's age higher or equal to 80 years
- Historical height loss more than 4 cm
- Self-reported but not listed former VF
- Glucocorticoid treatment equal to 5 mg of prednisone or higher or per day equivalent for 3 months or higher

Recommendations of the National and International Osteoporosis Foundation are mostly in accordance with the ISCD, taken a few additions into consideration. For instance the National Osteoporosis Foundation²¹ recommends in postmenopausal females and males older than 50 years with low trauma fracture during middle age (>50) or historical height reduction of 4 cm or more and potential height loss of 2 cm or more, or recent or ongoing long term glucocorticoid therapy.

Use of VFA in clinical practice

Vertebral fracture assessment technology has been exclusively designed in order to detect VF's, the diagnosis of which is of great importance in the osteoporosis detection

and treatment. VF's often represent the first osteoporotic fracture, as well as they also validate osteoporosis diagnosis, regardless of each individual's BMD²².

However, the majority of VF's are not clinically obvious²³. The undiagnosed fractures are not always asymptomatic but, on the other hand, they are often related to back pain and reduced activity. In addition, they are usually ignored by patients and doctors or attributed to other common diseases such as degenerative joint²⁴.

Furthermore, vertebral fracture assessment may be proved valuable to people with rheumatic diseases²⁵, particularly in rheumatoid arthritis and ankylosing spondylitis, in whom the presence of VF and osteoporosis is above average. Exceptional attention should be given to undertake such scans among those with more severe, active or prolonged disease, and those with a history of prolonged high dose glucocorticoid use²⁶.

A large study²⁷, showed that VF's identified on bone density vertebral fracture assessment images in clinical practice foresee incident hip, non-vertebral, major osteoporotic, and clinical VF's. The before mentioned study strongly supports the incorporation of targeted vertebral fracture assessment imaging at the time of bone densitometry to increase fracture risk evaluation and identification of postmenopausal females and older males at high risk of fracture.

VFA scans may show other irregularities, such as aortic calcification presence. The degree of calcification may be quantified to deliver an important mark of prevailing cardiovascular disorder, which provides cardiovascular events future prediction²⁸.

TBS (Trabecular Bone Score)

Definition

The Trabecular Bone Score is a textural index based on assessing the pixel gray-level variations in the lumbar dual-energy X-ray absorptiometry image as an innovative index of bone quality. The Trabecular Bone Score software has been approved for use by FDA in 2012. Applying Trabecular Bone Score measurements to clinical dual-energy X-ray absorptiometry images could be an efficient answer to the typical clinical assessment of TB microarchitecture.

Trabecular Bone Score is determined from the slope of the log-log transform of the 2D experimental variogram, relating gray-level variations in dual-energy X-ray absorptiometry images as a function of distance. A high value of TBS is directly correlated to better bone texture while a reduced value of TBS is related to weaker bone texture.

Trabecular Bone Score approximations normally are robust and independent from the dual-energy X-ray absorptiometry equipment, if the device is appropriately calibrated. The ability to evaluate TBS retrospectively using formerly acquired DXA images was influential in data collection validating with these the use in clinical practice²⁹⁻³¹.

Development of TBS

TBS was developed using two-dimensional projection images derived directly from three dimensional μ CT reconstruction of human cadaveric bone specimens. These early results showed substantial associations between Trabecular Bone Score and skeletal volume fraction, trabecular spacing, and trabecular number using cadaveric vertebral, femoral neck, and distal radius samples³¹.

Consequently, this method was extended to dual-energy X-ray absorptiometry images obtained ex vivo in cadaveric vertebrae. Various studies have presented noteworthy associations between TBS and various microstructural parameters of bone evaluated by microcomputed tomography.

It is tempting to speculate that TBS provides information on macroscopic parameters which, in turn, correlate with bone microstructure. This remains an area of active investigation. However, TBS has been shown to be a clinically useful tool due to its ability to assess fracture risk^{32,33}.

Factors that influence TBS values

Reported data³⁴ indicate that TBS values obtained for all lumbar vertebral combinations reduced with age. There is a linear decrease of 16 percent (~ -2.47 T-score) in the microarchitecture at L1-L4 between 45 & 90 years of age versus (-2.34 BMD). The microarchitecture rate of loss rises after the 65 years by 50 percent (from -0.004 up to -0.006).

Even though degenerative diseases of the lumbar spine are expected to affect values of TBS, there are publications³⁵ which propose that this effect is relatively small. It may be expected that there is vertebral exclusion is not needed for the calculation of TBS. In order to define the appropriate clinical approach, more fracture data studies are needed.

On the other hand, body weight and BMI have a major influence on TBS values. For example, in 82 women 12 to 41 years old, with anorexia nervosa, the values of TBS were reduced in the group with osteoporosis and directly related to parameters such as BMI, body weight and fat mass³⁶. Even though soft tissue thickness and BMI are taken into consideration while TBS is derived, the association between TBS and body weight proposes that TBS outcomes should be adjusted for BMI.

In addition, even more technical and clinical studies are essential for the determination of advantages and limitations of the TBS. These, may be proved useful in clinical practice as far as treatment decisions are concerned³⁷.

Fracture Risk Prediction by TBS

Several studies have displayed that TBS is used for fracture risk prediction in females and males. The Canadian province of Manitoba published a large study assessing TBS³⁸. A sum of 29407 women 50 years or older has been identified from a database containing all clinical results, at the time of baseline hip and spine DXA. TBS has been

correlated with many risk factors that predict fractures and considerably reduced spine TBS and BMD were identified in females with major osteoporotic, spine, and hip fractures (all $p < 0.0001$). Spine TBS and BMD predicted osteoporotic fractures equally fine, and the combination was superior to either measurement alone ($p < 0.001$). The TBS prediction on fracture risk has also been studied in 560 postmenopausal white females from the French (OFELY) cohort³⁹. Fractured women had, at baseline, reduced LS BMD and TBS than other without incident fractures.

Recent studies⁴⁰⁻⁴³ have shown correlation between LS TBS and vertebral, hip and other types of osteoporotic fractures to postmenopausal females. A more recent study from Leslie and colleagues⁴⁴ has shown that TBS is directly correlated to incident fractures in men. In addition, another study in men with limited data⁴⁵, has also confirmed the before mentioned statement.

Furthermore, recent studies^{46,47} have shown an enhancement in fracture estimation when TBS is used combined with FRAX. Recently published ISCD official reports⁴⁸ suggest that "TBS can be used in association with FRAX and BMD to adjust FRAX probability of fracture in postmenopausal women and older men."

Hip Structural Analysis

In the modern era, technological developments of DXA equipment may produce data for the determination of BMD, as well as the bone geometry parameters such as femoral size, shape, and strength. HSA (Hip Structural Analysis) and AHA (Advanced Hip Assessment) have been approved from the FDA in clinical use.

In addition, as far as the scanner is concerned, various parameters such as CSA (cross-sectional area), CSMI (the cross-sectional moment of inertia), BR (the buckling ratio), or SM (section modulus) may be acquired from DXA commercial scans.

Hip Structural Analysis and Advanced Hip Assessment estimate macro-architecture of the hip from the 2D DXA image and obtain parameters that are well known to be related to the fracture risk and the bone strength.

In addition, HAL (the hip axis length) which is defined as the distance from the inner-pelvic brim to the greater trochanter and NSA (the neck shaft angle), which is the angle between femoral neck axis and femoral mid-shaft axis, may be derived from a dual-energy X-ray absorptiometry image manually or automated^{49,50}.

Faulkner et al⁵¹ studied the Osteoporotic Fractures and presented that a longer hip axis length has been related to an increased risk of hip fracture in postmenopausal females. Following the study results in multiple populations, the hip axis length may predict hip fracture in postmenopausal females only⁵⁰.

The risk may not be quantified and as a consequence prior data acquired from the Manitoba database showed that the hip axis length was able to predict hip fractures with

adjustments and with a substantial development in total risk reclassification⁵².

Strong evidence indicates that the neck shaft angle may be able to predict hip fracture in postmenopausal females and males older than 60 years, with inadequate evidence that this risk is not dependent on BMD. On this purpose, no sufficient evidence prove that neck shaft angle may seem useful in clinical practice. Neck shaft angle, also differs by ethnicity and gender with a wider angle in males compared to females, and a higher one in Caucasians compared to Chinese⁵⁰.

Limitations

DXA scanners have also limitations concerning bone geometry parameters. Some are due to the irregularity of the proximal end of the femur and the fact that it rotates about the acetabulum, which is not located on its long axis⁵³. It has been noted that even minor rotational changes may produce a significant effect on the projected dimensions. The technologist cannot visually identify the femur and rotation of the leg is a matter that may affect the measurement.

Furthermore, another limitation of HSA is that scan images are often blurred so that edge margins can be difficult to locate precisely. Image quality problems tend to be higher with the fastest scan modes and in heavier patients. Also, due to the fact that DXA is two-dimensional, HSA can evaluate CSMI and section modulus only in the image plane. Many bone cross-sections are not axially symmetric, so these properties vary with rotation of the bone⁵⁴.

The use of Hip Geometry Parameter for the fracture risk prediction

The risk of hip fracture currently is well estimated by dual energy X-Ray absorptiometry (DXA) which is the most readily quantified skeletal strength measure method. Low BMD DXA has been established as fragility fracture risk factor but, on the other hand, the percentage of fracture risk as explained by bone geometry is considered unclear. For instance, Rotterdam cohort study⁵⁵ suggested that the result from the HSA (cortical thickness, section modulus narrow neck width, and buckling ratio) were no better than the ones derived from the predictive capability for hip fracture of BMD because the extreme thinning of cortices in expanded bones plays a key role on local susceptibility to fracture and this do not estimate with DXA yet.

On the contrary, Kaptoge et al⁵⁶ study of Osteoporotic Fractures (SOF), showed that proximal femurs of elderly women with hip fracture have lower bending (section modulus) and axial (CSA) strengths, with thinner more asymmetric cortices, and are wider in diameter than those of fracture-free women. These geometrical parameters provided better prediction of hip fracture risk than hip BMD.

The Manitoba study⁵⁷ provided data of 30953 woman aged 50 years hip DXA measurements, with 270 hip fractures during 3,7 years of observation. Only HAL and FSI

seemed to give a significant, though small, contribution to hip fracture prediction with no dependence on age and BMD measurement.

The importance of HAL, one of the first geometrical indexes, is still controversial. Although it is proposed as an indicator of proximal femur fracture risk for women, independent on FN BMD measurement⁵⁸. It is not always well considered as an independent risk factor⁵⁹. Recently, Leslie et al⁶⁰ demonstrated that HAL was an independent BMD and FRAX risk factor.

The 2015 ISCD guidelines, suggest that the small changes from baseline in hip structural parameters cannot be used for therapy effects monitoring in clinical practice. Neither HAL, nor NSA is expected to change with therapy, although the measurements were precise.

Many studies have shown that hip geometrical parameters are directly associated to the risk of hip fracture (particularly BR, SM, HAL, and NSA), but the risk cannot be quantified. On this purpose these parameters, at this time, cannot be used in order to initiate treatment in clinical practice.

Additional data and studies are needed in order to determine the quantification of the HAL effect for use in clinical practice, not only in postmenopausal women, but also in men, African Americans and more. Moreover studies with newer, better resolution DXAs, may expand the clinical utility of these measurement⁵⁰.

Conclusion

DXA can be used not only to measure BMD as well as for other additional tools such as TBS, VFA and HSA for a complete estimation of bone density and fracture risk.

The available scientific data for the use of TBS is promising. Preliminary data has shown that TBS can improve fracture prediction when used in combination with FRAX®. If further studies define TBS limits at age and gender, TBS could become a valuable clinical tool in the fracture risk assessment, helping to take therapeutic decisions especially to those who are at risk for fractures.

Based on the available data, VFA has already been incorporated into a number of clinical guidelines that replace the conventional X-ray to estimate prevalent vertebral fractures and therefore for the risk of fracture. The agreement between morphometric and morphological approaches for vertebral fractures 2 and 3 is high, but there is a felt inequality in mild grade 1 fractures.

Finally, hip structural analysis is an important factor in predicting hip fracture. Therefore, only BMD should not be considered clinically, but it is also important to carefully examine HSA to assess the risk of hip fracture.

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