Vertebral Fractures in Osteoporosis: A New Method for Clinical Assessment

Harry K. Genant, M.D., Jiao Li, M.D., Chun Y. Wu, M.D., John A. Shepherd, Ph.D.
Osteoporosis and Arthritis Research Group, Department of radiology,
University of California, San Francisco

ABSTRACT

Vertebral fractures are the most common consequence of osteoporosis, and are an important risk factor for subsequent fractures. Patients with reduced Bone Mineral Density (BMD) and vertebral fractures have significantly increased risk for future fractures, indicating great potential for the combined use of fracture assessment and BMD in risk evaluation. Despite the established importance of fractures, however, vertebral assessment is not typically performed in the clinical evaluation of patients at risk for osteoporosis. Radiographs are the accepted standard for assessment of fractures, but are rarely obtained in osteoporosis assessment for a variety of practical reasons, including cost, radiation dose, and the lack of office-based radiological facilities. Clinical assessment of fractures is difficult because most are asymptomatic. Consequently, this strong risk factor for osteoporotic fractures is often overlooked. High-resolution lateral spine images, obtained on a fan-beam Dual X-ray Absorptiometry (DXA) system, provide a practical, low-radiation dose, point-of-care methodology for assessment of vertebral fractures, and have the potential to address this important clinical need. The importance of vertebral fractures and the methods of assessing them are reviewed here. Clinical data supporting the feasibility of visual evaluation of lateral spine images obtained using a fan-beam DXA system are also reviewed, and the potential positive impact of this new methodology on clinical patient evaluation is discussed.

Prevalence of Vertebral Fractures

In the United States, it is estimated that 25% of females over age 50 have vertebral fractures,[1] and that the proportion of females with fractures increases rapidly with age (Fig. 1). By age 75, more than 1 in 3 women have at least one fracture. Based on these results, it is estimated that 7 million U.S. Caucasian women over the age of 50 have vertebral fractures.[1] The same study also estimated that new vertebral fractures occur in about 500,000 U.S. Caucasian women each year.

Using similar criteria for the definition of fractures, a large scale study (17,342 subjects) performed across Europe found fractures in 20% of Caucasian females over the age of 50.[2] In addition to the similar overall prevalence compared to U.S. results, the European studies also found a strong age dependent increase in fracture prevalence. Interestingly, 20% of U.S. and European males over the age of 50 were also found to have vertebral fractures, but with more of these fractures present at an earlier age, presumably due to traumatic events.[2,3]

Few studies have assessed the prevalence of vertebral fractures for other ethnic groups. Bauer estimated that the prevalence of fractures for Hispanic-American females is about one-half that of Caucasian females, or nearly 10% of this population over the age of 50.[4] Estimates suggest that vertebral fractures are less common for African-American men and women, with a prevalence of only a few percent.[5] Data for Japanese-American females suggests a prevalence similar to Hispanic-Americans, or about half that of Caucasian-American females.[6]

From these data, it is clear that vertebral fractures are present in a significant percentage of the population over the age of 50, and that a significant number of new fractures occur each year. Vertebral fractures are especially common in Caucasian women and men in Europe and in the United States, as well as in females of Hispanic and Japanese descent.

Vertebral Fractures and Risk for Subsequent Fractures

It is well established that the existence of a previous vertebral fracture increases the risk of subsequent fractures. Irrespective of a patient's BMD, a previous vertebral fracture increases risk significantly (Table 1).[6,7,8,9,10,11,12] In addition, it is also well established that risk for future fractures is increased for patients with low BMD. Nearly a decade ago, Ross demonstrated that the combination of BMD and vertebral fracture

A patient with "low" BMD and 1 vertebral fracture has a 25-fold higher risk for subsequent vertebral factures compared to a patient with "high" BMD and no fracture.

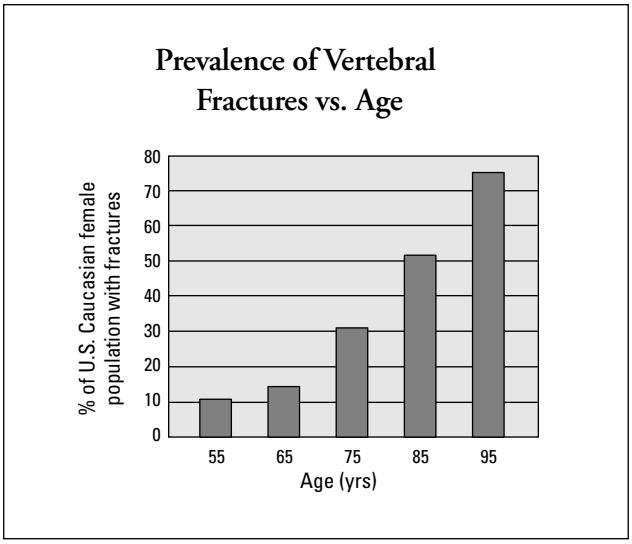

Fig. 1. The prevalence of vertebral fractures increases with age for Caucasian females, estimated by Melton.[1] Approximately 25% of all Caucasian females over the age of 50 have at least one vertebral fracture.

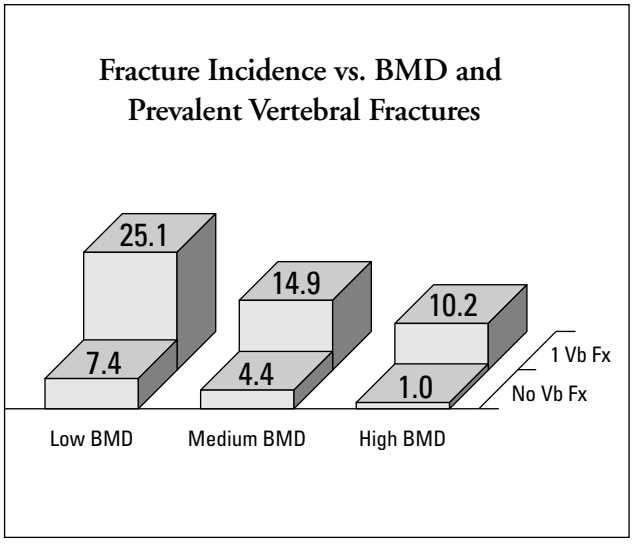

Figure 2. Risk for incident vertebral fracture based on current vertebral fracture status and BMD from Ross.[6] Prevalent fracture status and BMD are strong predictors of fracture risk, and can be combined for even stronger prediction of risk.

results yields an even stronger prediction of the risk of subsequent fractures (Fig. 2).[6] For example, a patient with "low" BMD and 1 vertebral fracture has a 25-fold higher risk for subsequent vertebral fractures compared to a patient with "high" BMD and no fracture.[6] Importantly, a patient with "medium" BMD and an existing vertebral fracture actually has *twice* the risk for subsequent fractures compared to a patient with "low" BMD and no fracture. Using only BMD results, as is the case in most clinical situations (without knowledge of vertebral fracture status) it is common practice to consider only those patients with "low" BMD to be at elevated risk. However, from Fig. 2 it is clear that even a patient with "high" BMD and a vertebral fracture is at slightly higher risk than the patient with low BMD but no fractures.

Table 1. Increase in risk for subsequent fractures, by fracture site, for subjects with existing vertebral fractures.[6-12]

Site of Subsequent Fracture	Increase in Risk due to Prevalent Vertebral Fracture
Vertebral	Four- to five-fold
Hip	Two-fold
Any	Three-fold

Not surprisingly, the presence of multiple vertebral fractures is associated with even higher risk (Fig. 3). A patient with low BMD and 2 or more fractures has 75 times the risk of a patient with high BMD and no fractures. From these data, it is clear that substantial improvements in risk assessment for individual patients can be achieved by combining BMD and vertebral fracture assessment.

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Patients with low bone density and vertebral factures are not only at highest risk, but also would benefit most from therapy.

Effectiveness of Osteoporosis Therapies in Patients with Vertebral Fractures

The central test of the efficacy of any therapeutic agent for osteoporosis is the prevention of fractures. For this reason, virtually all osteoporosis therapies have undergone fracture prevention trials. These clinical trials commonly include cohorts of post-menopausal females with existing vertebral fractures, especially because this group is expected to have an increased incidence of new fractures. In addition to being a true test of "treatment" of established disease (i.e., the subjects have already fractured at least once), the selection of this group has the benefit of increasing the statistical power of the study due to the high number of new fractures expected in this group. For these reasons, it is common for regulatory bodies to require a demonstration of fracture reduction in a population with vertebral fractures. As a result, clinical trials for osteoporosis therapies generally provide a direct demonstration of their effectiveness in patients with vertebral fractures (Fig. 4).

The results from pharmaceutical trials of the commonly available treatments for osteoporosis (Fosamax, Evista, Actonel, Estrogen) have broadly similar results,[13,14,15,16,17] demonstrating:

- 30% to 50% reductions in fracture incidence are observed in the treated groups.
- Larger therapy induced BMD increases are observed for those with lower initial BMD and vertebral fractures.
- Larger reductions in fracture incidence are generally associated with larger BMD response.
- Patients with existing vertebral fractures have a higher incidence of subsequent fractures than those without fractures.

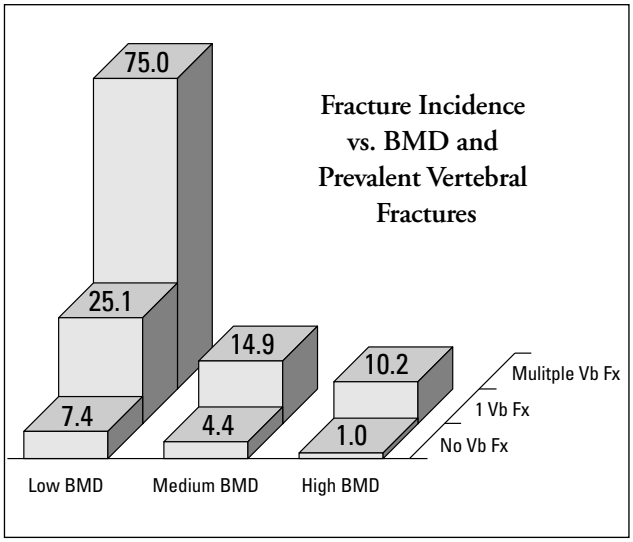


Figure 3. Risk for incident vertebral fractures based on current vertebral fracture status and BMD from Ross,[6] including multiple vertebral fractures. Data for multiple fractures with high and medium BMD were not reported by Ross, due to insufficient statistics.

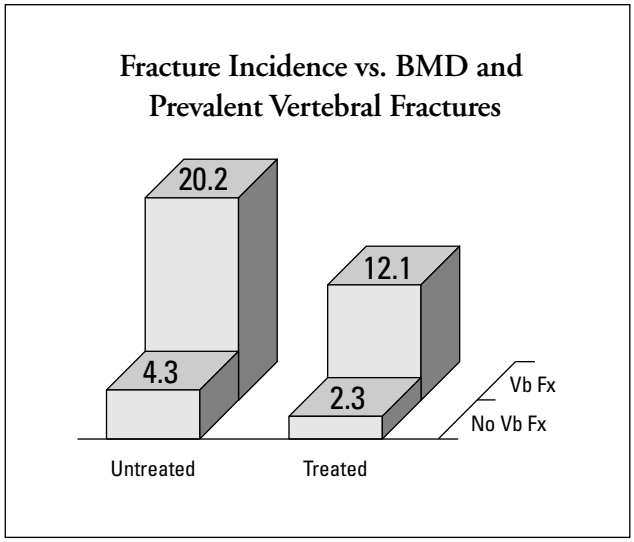


Fig. 4. Incidence of new vertebral fractures in treated (Evista) and untreated groups, classified by presence or absence of vertebral fractures at baseline.[16] Treatment reduces fracture incidence by about 50%, and the presence of a vertebral fracture at baseline increases risk five-fold.

The critical link between increased effectiveness (higher BMD response, lower fracture rates) and increased risk (lower initial BMD, existing vertebral fractures) has been established by these clinical trials. On the whole, the available osteoporosis therapies are most effective in reversing bone loss and preventing subsequent fractures for patients with low bone density and previous vertebral fractures (i.e., those at highest risk). Patients with low bone density and vertebral fractures are not only at highest risk, but also would benefit most from therapy.

Clinical Identification of Vertebral Fractures

Although vertebral fractures are common in post-menopausal women, they are difficult to identify clinically (i.e., without radiographs). Large-scale prospective studies indicate that only about 1 in 4 vertebral fractures are clinically recognized.[18] The lack of clinical recognition of fractures is due to both the absence of symptoms and to the difficulty in determining the cause of symptoms, which may have a variety of origins. For example, it has been estimated that less than 1% of episodes of back pain are related to vertebral fractures.[19] As a result, vertebral fractures are not commonly suspected in patients reporting back pain, unless the back pain is associated with trauma. Trauma related fractures, of course, are not considered classical (atraumatic) osteoporotic fractures. In osteoporosis evaluation, the likelihood of back pain being considered as evidence of vertebral fracture is even more remote.

Height loss, another indicator of vertebral fractures, is also difficult to assess clinically. Some height loss is expected with aging, due to compression of the intervertebral discs and postural changes. Studies have concluded that height loss is an unreliable indicator of fracture status until it exceeds 4 cm.[20]

Large-scale prospective studies indicate that only 1 in 4 vertebral fractures are clinically recognized.

Unfortunately, a loss of 4 cm could also be due to multiple fractures, at which point there is significant and irreparable damage.

It is for these reasons that only 1 in 4 vertebral fractures is clinically recognized. As a result, vertebral fractures are rarely considered in clinical patient evaluation, and it is uncommon for patients to be referred for radiographs in the course of osteoporosis testing.

Radiographic Identification of Fractures

The use of radiographic techniques for general fracture identification is well established. Radiographic evaluation of vertebral body fractures is equally well established.[21,22] Standard radiographic techniques for evaluation of the vertebrae of the thoracolumbar spine involve the acquisition of 4 views, with thoracic and lumbar films obtained in both the AP and lateral projections. Identification of fractures is typically performed by visually assessing vertebral shapes, relying on the radiologist's training for accuracy in fracture identification. Vertebrae are classified as "fractured" or "non-fractured" based on the qualitative evaluation of alterations in vertebral morphology. Vertebral fractures, like fractures at most other skeletal sites, are manifested by a variety of different types of shape changes (Fig. 5), including "wedge," "crush," or "bi-concavity." In addition, the degree of "wedging," "crushing," or "bi-concavity" is variable in vertebral fractures, depending on the circumstances (trauma, osteoporosis, etc.). In order to improve the evaluation, classification, and description of vertebral fractures in clinical trials and epidemiological studies, grading techniques have been developed, and the term "deformity" is frequently used.[23] These grading or classification techniques describe the type of deformity, and its severity. A deformity is considered a fracture if visual inspection indicates a reduction in vertebral height (anterior, posterior, or middle) of 20-25% or more.[23] The "semi-quantitative" method of grading deformities distinguishes fractured vertebrae (grades 1, 2, and 3, as in Fig. 5) from non-fractured vertebrae (deformities that do not reach the level of grade 1).

Classification schemes can also be used to identify fractures and degrees of deformity quantitatively.[24] Quantitative evaluation is performed by marking the vertebral endplates and measuring shape parameters such as vertebral heights, vertebral area, etc.[24] Quantitative deformity assessment is especially useful in pharmaceutical trials, where objective evaluation is preferred,[25,26,27,28] but studies have found that similar results are obtained by visual and quantitative methods when similar criteria are employed.[25,29,30] Visual radiographic identification of vertebral fractures remains the gold standard, and is considered the preferred means for identification or confirmation of the presence of osteoporosis in clinical practice.

Alternatives to Radiographic Assessment

The use of high-resolution lateral spine images, obtained with fan-beam X-ray bone densitometry systems (Fig. 6), offers a potential practical alternative to radiographs for clinical vertebral fracture analysis. High-resolution fan-beam DXA systems, utilizing technology similar to that used by computed tomography (CT) systems, can image the lateral spine in as little as 10 seconds. In fact, CT scout scans, with about the same image resolution as fan-beam DXA scans, have been used for vertebral fracture identification.[31,32,33] Like radiographs, however, computed tomography images are expensive and are not available clinically without referral. Consequently, CT is not a practical option. In contrast, DXA images can be performed at the point of care, in conjunction with standard BMD determination, with a radiation dose as much as 100 times lower than that of conventional radiographs. The relative strengths and weaknesses of radiographs and DXA images are summarized in Table 2. The most notable strength of radiographs, of course, is image resolution, which is superior to that of DXA images.

DXA images can be performed at the point-of-care, in conjunction with standard BMD determination, with a radiation dose as much as 100 times lower than that of conventional radiographs.

Because the DXA spine images are acquired and stored electronically, an image of the entire spine can be presented in a single view, making it possible to magnify particular areas of interest, and brightness and contrast of the image can be adjusted and optimized interactively. Using radiographic techniques, separate films of the lumbar and thoracic regions are required, and images cannot be manipulated to compensate for variations in technique. Newer digital radiography, while expensive, does provide this electronic capability. Cone-beam distortion, inherent in the radiographic technique, is not present when using the scanning fan-beam geometry of DXA devices. In addition, images obtained on a DXA system can be electronically archived and reviewed side-by-side with images obtained at follow-up examinations.

While the image resolution of conventional radiographs is superior to fan-beam DXA, there is a growing body of literature reporting the utility of DXA images for visual and quantitative evaluation of vertebral fractures.[34,35,36,37,38,39] The possibility of visual evaluation of fan-beam DXA images was first

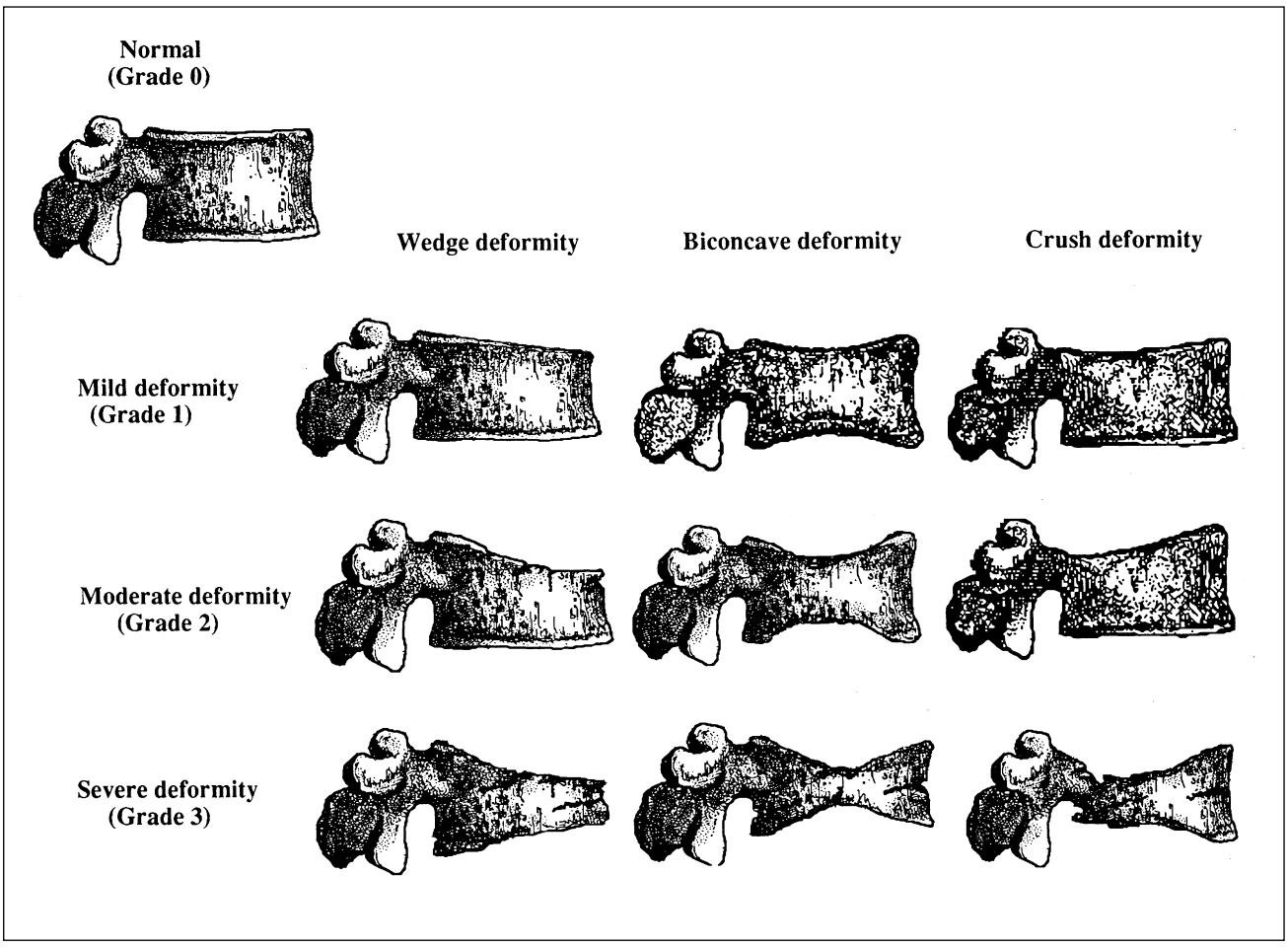
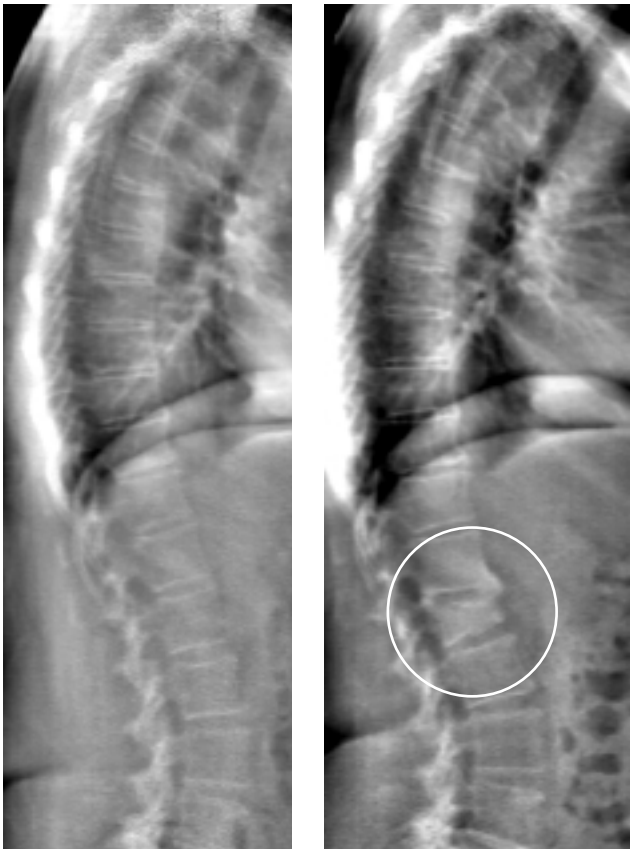


Fig. 5. Classification of vertebral fractures by the Genant semi-quantitative method.[23]



Baseline **2 year Follow-up**

Figure 6. Rapid (10 second), high-resolution imaging with a fan-beam system allows visual assessment of vertebral fractures. A wedge fracture, not present in the baseline examination, is clearly seen in the follow-up study, 2 years later.

reported by Hans et al.,[37] who found excellent agreement with qualitative radiographic assessment in a preliminary study using fan-beam dual-energy DXA images. Lang et al.[38] reported excellent visualization of vertebrae from fan-beam dual-energy DXA images in a small (n=16) post-menopausal female population. Using a Hologic QDR 4500 system, Rea et al.[39] showed that high-speed fan-beam DXA imaging was feasible in a clinical population, allowing visualization of a substantial proportion of the vertebrae, using a rapid (10 second) single-energy imaging mode (Fig. 6). Low-dose, single-energy acquisition modes are substantially faster than dual-energy scan modes, due to substantially lower signal to noise in the images, and can be performed during suspended respiration.

Visual identification of fractures is attractive, particularly in the clinical environment, because quantitative morphometric analysis is a time consuming procedure.

Table 2. Comparative Characteristics of Radiographs vs. Fan-beam DXA Imaging in Vertebral Fracture Assessment.

Parameter	Radiographs	Fan-beam DXA Imaging
Image resolution	5 lp/mm	0.5 – 1 lp/mm
Radiation Dose	800 µSv	< 10 µSv
#Lateral Images Required to Cover L4 – T4	2	1
Imaging Geometry	Cone-beam	Fan-beam
Cone Beam Distortion	Yes	No
Single-Energy Imaging w/ breath hold	Yes	Yes (10 second acquisition)
Electronic acquisition/storage	No*	Yes
On screen viewing/ manipulation	No*	Yes
Side-by-side viewing of baseline and follow-up images	No*	Yes
Point-of-Care Availability	No	Yes

**Yes for the newer, digital radiography systems.*

Overall agreement, including even mild fractures, is approximately as strong as that found between different radiologists, indicating that image quality allows effective evaluation of fractures.

Feasibility of Visual Evaluation of Lateral Spine DXA Images

The use of fan-beam DXA images for quantitative (morphometric) assessment of spinal fractures has been reported in both research applications and pharmaceutical trials.[25,34-41] Interest in morphometric assessment from DXA images was a natural consequence of the need for quantitative fracture evaluation in pharmaceutical trials. Since BMD was already being assessed by DXA on subjects enrolled in these trials, the possibility of quantitative DXA morphometry was particularly attractive, given the convenience and minimal radiation dose. Based on the experience gained in these studies, it was noted that visualization of vertebrae in fan-beam DXA images is sufficient to visually evaluate fractures. Visual identification of fractures is attractive, particularly in the clinical environment, because quantitative morphometric analysis is a time consuming procedure, typically performed by a highly-skilled operator.

Subsequently, clinical studies have demonstrated the feasibility of visual evaluation of fan-beam lateral DXA spine images in post-menopausal females.[39,40,41] Lateral spine images were obtained using a Hologic ***QDR 4500*** system for 161 post-menopausal female subjects, and were visually evaluated for presence or absence of fractures.[40,41] Lateral radiographs were also obtained, and read by an experienced radiologist using the Genant semiquantitative technique. ***QDR 4500*** images permitted visual assessment of 95% of all vertebrae. Vertebrae that could not be visualized were predominantly at the T4

and T5 levels, where relatively few osteoporotic fractures are found. For the 95% of the vertebrae that could be visualized, sensitivity and specificity for moderate to severe fractures were excellent (92% and 96%, respectively). The negative predictive value for these fractures was 99.4%, indicating that moderate to severe vertebral fractures can be ruled out with high confidence. Even including mild (grade 1) fractures, visual evaluation of DXA images had high negative predictive value (97.5%), and reasonable sensitivity (77%) and an excellent specificity (98%). A strong overall agreement (96.3%) was found between visual evaluation of DXA images and radiographic results, with a Kappa score of 0.79. The Kappa score accounts for random, or chance agreement, and is considered a more rigorous test of concurrence.[42] A Kappa score of 0.81 or higher is considered "excellent."[43]

The clinical studies indicate that visual evaluation of fractures, based on lateral spine images obtained on the ***QDR 4500*** fan-beam densitometer, is feasible in the at-risk population. The agreement between visual evaluation of DXA images and radiographs is particularly strong for moderate to severe fractures, which are the most clinically important. The overall agreement, including even mild fractures, is approximately as strong as that found between different radiologists,[44] indicating that image quality allows effective evaluation of fractures.

NOF and IOF clinical guidelines indicate vertebral fractures are the key risk factor, other than low BMD, in the assessment of risk.

Discussion

Under the current standard of care, women who are at risk for osteoporosis and osteoporotic fractures are referred for bone density testing. Based on individual risk factors and the results of the bone density exam, the physician will decide if the patient is a candidate for therapeutic intervention or other preventive measures. Most clinical guidelines, including those from the National Osteoporosis Foundation (NOF)[45] and the International Osteoporosis Foundation (IOF),[46] indicate that vertebral fractures are the key risk factor, other than low BMD, in the assessment of risk. The importance of fragility fractures, of which vertebral fractures are the most common example, was recognized in the World Health Organization (WHO) classification criteria for osteoporosis evaluation.[47] The WHO criteria defines "severe osteoporosis" as low bone mass "in the presence of one or more fragility fractures."

Because of the difficulty in identifying vertebral fractures clinically, and the practical difficulties preventing radiographic assessment at the point of care, vertebral fracture status is infrequently known at the time of patient evaluation. Given that a significant proportion of women over the age of 50 have vertebral fractures, and that the presence of these fractures puts them at substantially increased risk, it is clear that there is an important opportunity for improvement in patient evaluation. Increased availability of effective clinical tools for assessment of vertebral fractures provides the means for improved patient evaluation, and enhances the physician's ability to target therapeutic intervention to those who would benefit most.

In contrast to older generation DXA devices, which had poorer resolution and long scan times, state-of-the-art fan-beam DXA devices are capable of obtaining fast, high resolution images useful for visual fracture evaluation.

Clinical studies, involving post-menopausal female subjects, have shown that fan-beam DXA images obtained on Hologic fan-beam bone densitometers can be used for either quantitative or visual evaluation of vertebral fractures. In contrast to older generation DXA devices, which had poorer resolution and long scan times, state of the art fan-beam DXA devices are capable of obtaining fast, high-resolution images useful for visual fracture evaluation. In the region from vertebral level L4 – T7, where the vast majority of fractures occur, nearly all vertebrae are visualized and can be evaluated. When compared to the gold standard, radiographs, the sensitivity and specificity of visual evaluation are high, especially for moderate to severe fractures (92% and 96%, respectively). The excellent negative predictive value (99.4%, for moderate to severe fractures) indicates that vertebral fractures can be ruled out with high confidence. The observed agreement between visual evaluation of DXA images and visual evaluation of radiographs by an experienced radiologist was strong ($k = 0.79$), and is approximately as good as that observed between different radiologists.

In addition to improved risk stratification, the evaluation of vertebral fractures also has important consequences when therapeutic intervention is contemplated. Documentation of vertebral fractures can reduce the widely recognized problems of lack of acceptance and long term compliance with therapies. The demonstrated effectiveness of available therapies, coupled with the possibility of improved acceptance and compliance could yield important benefits to women's health.

The visual evaluation of vertebral fractures using fan-beam DXA images is an important step forward in the clinical evaluation of patients at risk for osteoporosis.

For these reasons, the visual evaluation of vertebral fractures using fan-beam DXA images is an important step forward in the clinical evaluation of patients at risk for osteoporosis.

Conclusions

Vertebral fractures are the most common consequence of osteoporosis, occurring in a substantial portion of the post-menopausal population. Most vertebral fractures, however, are not clinically recognized, and can accumulate silently. It is established that the presence of a vertebral fracture is a strong risk factor for subsequent osteoporotic fractures, and that those with low bone density and vertebral fractures are

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at highest risk. Large-scale clinical trials have demonstrated that osteoporosis therapies can reverse bone loss and reduce fracture rates, and that these benefits are most pronounced in patients with low BMD and vertebral fractures. Clinical guidelines promulgated by the NOF, IOF, and WHO recognize the importance of vertebral fractures, along with BMD, as the key risk factors for use in patient evaluation. However, while BMD is widely used in patient evaluation, assessment of vertebral fractures is not commonly performed, primarily due to practical limitations associated with referral for radiographs.

The integration of BMD and vertebral fracture assessment in a clinical environment has multiple benefits, including improved risk assessment, improved selection of candidates for intervention, and the potential for improved patient understanding of the consequences of osteoporosis.

The availability of a rapid, low-dose, point-of-care method for assessment of vertebral fractures, using advanced, state-of-the-art DXA devices, provides a practical means for integrated assessment of BMD and vertebral fracture status. This technology provides lateral spine images that allow visual identification of most fractures, enabling point-of-care evaluation of fractures and BMD. The integration of BMD and vertebral fracture assessment in a clinical environment has multiple benefits, including improved risk assessment, improved selection of candidates for intervention, and the potential for improved patient understanding of the consequences of osteoporosis. Improved patient understanding is an important consideration in osteoporosis evaluation, due the "silent" nature of bone loss. In particular, documentation of the presence of fractures provides the opportunity for improved patient acceptance of therapeutic intervention, and long-term compliance with treatment. Visual vertebral fracture evaluation, using lateral spine images obtained using a DXA device, can significantly improve osteoporosis risk evaluation. The combined evaluation of vertebral fracture status and BMD is likely to become the new standard for patient evaluation, particularly in older post-menopausal women for whom vertebral fractures are common.

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