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Horizon Scanning Technology Prioritising Summary

Vertebral assessment with DEXA

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PRIORITISING SUMMARY

REGISTER ID: 000209

NAME OF TECHNOLOGY: VERTEBRAL ASSESSMENT WITH DEXA

PURPOSE AND TARGET GROUP: SCREENING FOR VERTEBRAL FRACTURE DURING RISK ASSESSMENT FOR OSTEOPOROSIS

STAGE OF DEVELOPMENT (IN AUSTRALIA):

- | | |
|---|--|
| <input type="checkbox"/> Yet to emerge | <input type="checkbox"/> Established |
| <input type="checkbox"/> Experimental | <input checked="" type="checkbox"/> Established <i>but</i> changed indication or modification of technique |
| <input type="checkbox"/> Investigational | <input type="checkbox"/> Should be taken out of use |
| <input type="checkbox"/> Nearly established | |

AUSTRALIAN THERAPEUTIC GOODS ADMINISTRATION APPROVAL

- | | |
|---|-------------|
| <input type="checkbox"/> Yes | ARTG number |
| <input checked="" type="checkbox"/> No | |
| <input type="checkbox"/> Not applicable | |

INTERNATIONAL UTILISATION:

COUNTRY	LEVEL OF USE		
	Trials Underway or Completed	Limited Use	Widely Diffused
United States	✓		
United Kingdom	✓		

IMPACT SUMMARY:

This prioritising summary investigates the effectiveness of dual energy X-ray absorptiometry (DEXA) in diagnosing vertebral fracture. The summary also investigates the health benefits of screening for vertebral fracture during risk assessment for osteoporosis.

BACKGROUND

Vertebral fracture is a serious health issue amongst the elderly with the condition associated with increased morbidity and mortality. The most notable risk factor for vertebral fracture is osteoporosis, a disease of the bone in which bone mineral density (BMD) is significantly diminished. The World Health Organization defines osteoporosis as a BMD measurement of 2.5 or more standard deviations below the mean BMD of healthy young adults (expressed as a T-score), as measured by DEXA. The presence of a vertebral fracture, independent of BMD, has also been shown to be predictive of future fracture risk (Klotzbuecher et al 2000). The identification of vertebral fracture in patients without osteoporosis, as defined by their T-score, may help to target additional individuals who will benefit from anti-fracture therapy. Unfortunately, it has been estimated that less than a third of vertebral fractures are diagnosed and treated by medical practitioners (Cooper et al 1992). A large proportion of vertebral fractures go unnoticed because the symptoms are often not strong enough to warrant clinical investigation.

The standard method for diagnosing vertebral fractures is through the visual assessment of spinal lateral X-rays (produced using radiography) by either a radiologist or appropriately trained clinician. X-rays are assessed using one of a variety of grading systems, the most common being the semiquantitative method described by Genant (1993). There are three grades of vertebral deformity in the system, all related to the ratio of the anterior/posterior (AH/PH) and median/posterior (MH/PH) height. Grade one represents a 20 to 25 per cent reduction in any one ratio, grade two a 25 to 40 per cent reduction, and grade three a reduction of 40 per cent or more in any one ratio. The system allows for rapid assessment in the clinical setting, and unlike fully quantitative approaches, is capable of identifying false-positive vertebral fracture resulting from artefacts such as Scheuermann's disease (Duboeuf et al 2005). Despite being considered as a gold standard in the diagnosis of vertebral fracture, spinal lateral X-rays have not been recommended as a regular component of risk assessment for fracture. The primary reasons for this are the high costs and significant radiation dosages associated with radiography. It is typically reserved for patients either diagnosed with osteoporosis or reporting symptoms highly suggestive of vertebral fracture.

More recently, spinal imaging using DEXA has become available. Like radiography, the X-rays produced by DEXA can be assessed using a number of grading systems, including the semiquantitative method. Although the image quality is inferior, DEXA offers a number of advantages over standard radiography, including lower costs and radiation exposure (less than 40 μ Sv compared to 800 μ Sv from a spinal lateral x-ray), and greater convenience since the imaging can be performed at the same time as BMD measurement. For these reasons, many have recommended vertebral assessment by DEXA be performed in conjunction with the measurement of BMD as part of a standard fracture risk assessment. In clinical practice, such an approach may be particularly valuable in identifying fractures in patients with osteopenia or low bone mineral density (BMD T-score between -1 and -2.5) who otherwise would not be considered for anti-fracture therapy.

CLINICAL NEED AND BURDEN OF DISEASE

Osteoporosis is often referred to as a silent disease. Gradual loss of bone mass and deterioration of bone microarchitecture results in an increased susceptibility to fracture, often with little or no symptoms until the fracture occurs. Approximately 300,000 Australians have been diagnosed with osteoporosis, although many more have the condition without knowing it (DHA 2005). In 2001 it was estimated that more than 1.9 million Australians were suffering from osteoporosis and that this number would rise to three million by 2021 (Access 2001). In all age groups the prevalence of osteoporosis is higher in females than in males (Access 2001).

Studies have shown that fracture incidence rates increase exponentially with age, an occurrence attributable to age-related decreases in BMD and increases in the number of falls (Cummings & Melton 2002). Of those Australians aged 60 years and over, more than 50 per cent of women and 30 per cent of men suffer a fracture due to osteoporosis (DHA 2005). The total number of fractures sustained each year by Australians aged 60 years and over has been estimated to be between 51,000 and 73,000 (Sambrook et al 2002). Of all diagnosed osteoporotic fractures, 46 per cent are in the vertebral region (Access 2001).

A number of studies have demonstrated that the existence of a prevalent vertebral deformity increases the risk of further fracture two- to fivefold, independent of BMD (e.g. Klotzbuecher et al 2000). It has also been estimated that 20 per cent of patients who suffer a vertebral fracture experience a subsequent fracture within a year of the first (Brown & Josse 2002). In addition to further fracture, vertebral fractures have been associated with loss of stature, kyphosis, back pain, functional impairment, depression and higher mortality rates (Cummings & Melton 2002). Despite these adverse outcomes, it has been estimated that less than a third of vertebral fractures come to the attention of medical practitioners (Cooper et al 1992).

DIFFUSION

DEXA is used extensively in clinical practice for the assessment of BMD. To perform vertebral fracture assessment on the various DEXA devices, additional software is required. To date, no DEXA devices have received marketing approval from the TGA for the purposes of vertebral fracture assessment. In the United States, DEXA devices that have received FDA approval for fracture assessment include GE LUNAR Corporation's Dual Energy Vertebral Assessment (DVA™) and Hologic's Instant Vertebral Assessment™

COMPARATORS

Radiography is currently considered the gold standard for the assessment of vertebral fracture. Although radiography offers superior image quality over DEXA, it is not a candidate for routine fracture risk assessment due to the high costs and radiation dosages involved. At present, fracture risk assessment is achieved using BMD measurements alone (Sambrook et al 2002).

EFFECTIVENESS AND SAFETY ISSUES

The most significant limitation of DEXA in screening for vertebral fracture is the poor image quality of the upper thoracic vertebrae. Visualisation of vertebral bodies in the T4 to T6 region is severely diminished due to the presence of ribs and increased X-ray spill over attributable to lung tissue in the area (Duboeuf et al 2005). As a result, fractures in this region often go undetected. In studies investigating the diagnostic qualities of DEXA, between 5 and 15 per cent of vertebrae are generally excluded from analysis due to poor image quality. A recent study by Binkley et al (2005) (level III-2 diagnostic evidence) of 80 postmenopausal women found that while 95 per cent of vertebrae from T7 to L4 were evaluable, a majority of vertebrae in the T4 to T6 region (66%) were not adequately visualised. Although the exclusion of poorly visualised vertebrae should be taken into account when assessing the diagnostic value of DEXA, it is worth noting that vertebral fractures in the T4 to T6 region are relatively uncommon (Melton et al 1989).

A number of studies have assessed the diagnostic accuracy and inter-rater reliability of DEXA scans for detecting vertebral fracture. Rea et al (2000) (level III-2 diagnostic evidence) compared DEXA scans to conventional spinal lateral radiographs in a group of 161 postmenopausal women, including those with normal BMD and those with multiple vertebral deformities. According to their DEXA scan, participants were divided into normal, equivocal and definite deformity groups. DEXA and radiography demonstrated good agreement (96.3%, $\kappa = 0.79$) in classifying vertebrae as either normal or deformed. DEXA also demonstrated good sensitivity (91.9%) in identifying moderate/severe vertebral deformities as shown by radiography, and an excellent negative predictive value (98%) when used to identify subjects without vertebral deformity. In another study, Schousboe and Debold (2006) (level III-2 diagnostic evidence) compared DEXA scans to radiography in a group of 205 women aged 65 years and over. In the study, the authors were interested in assessing the diagnostic qualities of DEXA and whether they would be affected by the presence of disc space osteoarthritis, a condition common amongst the elderly. Excluding participants with scoliosis, the sensitivity and specificity of DEXA in detecting participants with one or more grade 2-3 deformities, as detected by radiography, was 87-93 and 93-94 per cent respectively. Although osteoarthritis was not shown to affect sensitivity, it did have a substantial impact on reliability. Using the entire sample, the inter-rater reliability for detecting a grade 2-3 deformity was acceptable for both radiography ($\kappa = 0.73$) and DEXA ($\kappa = 0.64$). After excluding participants with disc space osteoarthritis, the inter-rater reliability improved for both radiography ($\kappa = 0.76 - 0.82$) and DEXA scans ($\kappa = 0.70 - 0.78$).

Ferrar et al (2000) (level III-2 diagnostic evidence) compared DEXA scans to radiography in a group of 327 women, including 83 who had been diagnosed with osteoporosis. Using the

entire sample, inter-rater reliability was moderate to poor for both radiography ($\kappa = 0.59$) and DEXA ($\kappa = 0.47$). In the osteoporotic group however, inter-rater reliability improved for both radiography ($\kappa = 0.86$) and DEXA ($\kappa = 0.79$). Treating radiography as the gold standard, DEXA demonstrated reasonable sensitivity (72 to 82%) and negative predictive value (90%) in the osteoporotic patients. The sensitivity dropped considerably however when the entire sample was considered (54 to 58%). Across this and a number of other studies, the diagnostic qualities of DEXA have been noted to vary according to the prior probability of fracture in the studied population (Duboeuf et al 2005). In general, the lower the probability of fracture in the studied population, the lower the sensitivity of the test is likely to be. Given that screening tests require high levels of sensitivity in order to rule out a positive diagnosis, it is likely that DEXA will only be appropriate for routine screening in subgroups which have a higher likelihood of fracture (Duboeuf et al 2005).

In addition to requiring satisfactory diagnostic qualities, a program of routine screening with DEXA as an adjunct to BMD measurement should be capable of identifying additional patients at risk of future fracture who would otherwise not be considered for anti-fracture therapy. Several studies have addressed this issue. Greenspan et al (2001) (level IV diagnostic evidence) investigated the prevalence of vertebral fracture, as measured by DEXA, in 482 asymptomatic postmenopausal women being screened for an osteoporosis study. Vertebral fractures were discovered in 18.3 per cent of women in the study. In the absence of DEXA scans, between 11 and 19 per cent of clinically osteoporotic patients (defined by a T-score of less than -2.5 or the presence of a low impact fracture) would have been classified as normal using BMD measurements alone. In a similar study, Vokes et al (2003) (level III-2 diagnostic evidence) obtained DEXA scans and measured BMD in a sample of 297 participants (272 women). Evidence of vertebral fracture was found in 55 subjects, of which only 56 per cent would have met the criteria for osteoporosis using BMD measurements alone. The results indicate that DEXA screening is a useful adjunct in the identification of clinical osteoporosis, providing a more comprehensive fracture risk assessment than would be afforded by the measurement of BMD alone.

COST IMPACT

At this stage, DEXA devices have not received marketing approval from the TGA to be used for the purpose of vertebral fracture assessment. As a result, the cost of the relevant software is currently unknown.

The cost impact of a routine program of vertebral fracture assessment in a high-risk population is currently unknown. It is possible however, that the additional costs associated with vertebral fracture assessment would be outweighed by a reduction in the number of spinal lateral X-rays required and cost savings associated with the prevention of future fractures.

ETHICAL, CULTURAL OR RELIGIOUS CONSIDERATIONS

No issues were identified/raised in the sources examined.

OTHER ISSUES

An important issue in evaluating the effectiveness of a program of vertebral assessment using DEXA is the benefit associated with treating osteopenia patients (BMD T-score between -1 and -2.5) diagnosed with one or more vertebral fractures. Presumably it would be this group of patients and not patients with osteoporosis who would benefit from a routine screening program for vertebral fracture. Therapies currently available for the prevention of osteoporotic fractures include calcium and vitamin D supplementation, fall prevention education and antiresorptive drugs such as bisphosphonates (Access 2001). At present however, it is unclear whether any of these preventative strategies are effective in patients

with BMD T-scores between -1 and -2.5. While a number of large-scale trials on bisphosphonates have included patients with low BMD and prevalent vertebral deformities (e.g. Ettinger et al 1999), separate results for this subgroup have not been reported.

RECOMMENDATION:

A program of screening for vertebral fracture using DEXA offers a number of potential health benefits. In an appropriate high risk subgroup, DEXA vertebral assessment may be particularly useful in identifying fractures in patients who would otherwise not have been considered for therapy. Advantages of DEXA include its convenience, low radiation dosage and low costs. In high-risk subgroups, DEXA has also exhibited high levels of sensitivity in the detection of vertebral fracture, an important property in any screening program. Despite the potential benefits of DEXA fracture assessment, a number of questions remain unanswered. In addition to uncertainty regarding the cost impact of vertebral fracture screening, it is not currently known whether anti-fracture therapy is beneficial for patients with low BMD. A further unresolved issue is precisely what population subgroup a screening program should apply to. Given these uncertainties, it is recommended that the following be conducted:

- | | |
|--|--|
| <input type="checkbox"/> Horizon Scanning Report | <input type="checkbox"/> Full Health Technology Assessment |
| <input checked="" type="checkbox"/> Monitor | <input type="checkbox"/> Archive |

SOURCES OF FURTHER INFORMATION:

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- Melton, L. J., 3rd, Kan, S. H. et al (1989). 'Epidemiology of vertebral fractures in women', *Am J Epidemiol*, 129 (5), 1000-1011.
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- Sambrook, P. N., Seeman, E. et al (2002). 'Preventing osteoporosis: outcomes of the Australian Fracture Prevention Summit', *Med J Aust*, 176 Suppl, S1-16.
- Schousboe, J. T. & Debold, C. R. (2006). 'Reliability and accuracy of vertebral fracture assessment with densitometry compared to radiography in clinical practice', *Osteoporos Int*, 17 (2), 281-289.
- Vokes, T. J., Dixon, L. B. & Favus, M. J. (2003). 'Clinical utility of dual-energy vertebral assessment (DVA)', *Osteoporos Int*, 14 (11), 871-878.

LIST OF STUDIES INCLUDED

Total number of studies	6
Level III-2 evidence	5
Level IV evidence	1

SEARCH CRITERIA TO BE USED:

Densitometry, X-Ray/methods
 Thoracic Vertebrae/injuries/radiography
 Bone Density
 Absorptiometry, Photon/*methods
 Lumbar Vertebrae/pathology/radiography/*radionuclide imaging

AUGUST 2007 – UPDATE

NOTE: The original prioritising summary used the acronym DEXA for dual energy X-ray absorptiometry. While this is used in published literature, the majority of publications use the acronym DXA. This more prevalent terminology will be used in this update.

AUGUST 2007 COMPARATORS:

Ultrasound is a potential alternative technique used to assess bone mineral density (BMD) and also the presence of vertebral fractures. A study comparing DXA to ultrasound for measuring cadaver vertebral BMD and failure load, reported that ultrasound was at least as effective at predicting bone failure values as DXA determined BMD¹. As ultrasound is safer and easier to deliver to the patient this may be a future direction for BMD and vertebral assessment (Nicholson & Alkalay 2007). Another study investigating the ability of quantitative ultrasonometry (QUS) of the Calcaneus (heel) and DXA to predict morphometric fractures in the vertebrae of postmenopausal women, found that QUS and DXA could equally discriminate between women with and without vertebral fractures. This study included 764 women with non-traumatic vertebral fractures and 770 normal control women. DXA was used to determine BMD at several sites in each subject (total body, lumbar spine, total femur, femoral neck). Various combinations of QUS and BMD values were assessed with respect to increasing the predictive power for detecting vertebral fractures. No combination of parameters was found to exceed the predictive power of individual parameters. This indicates that ultrasonometry is a viable competitor for the predictive assessment of vertebral fractures in postmenopausal women (Frediani et al 2006).

AUGUST 2007 SAFETY AND EFFECTIVENESS ISSUES:

The ideal body site on the patient that gives the best BMD assessment is still being debated within the field of DXA vertebral assessment. The vertebral column would seem an obvious place to perform assessment but this is often precluded by the presence of X-ray anomalies that obscure or invalidate the direct assessment of particular vertebrae. A study on 460 subjects (mean age 73 ± 5.2) compared DXA-determined BMD at the lumbar spine and the hip. A combination of these values was also assessed. The hip BMD value was found to show the best correlation with osteoporosis and also the best correlation with prevalent vertebral fracture in the population studied (Arabi et al 2007)(diagnostic evidence level IV).

¹ When quantitative ultrasound and DXA are used to measure bone strength they can both give a prediction of when the bone will fail under mechanical stress.

Whether DXA is useful in all patient subgroups and what variability can be expected for the same patient in multiple scans was addressed in a study published in 2006. The study reported that sampling greater bone area improved the precision of DXA, that is, the ability of multiple scans of the same subject to be interpreted to give the same results by different clinicians. Where there was more variability in the population BMD, e.g. in elderly populations, there was a greater negative impact on the precision of the DXA scans. The authors therefore recommended that each facility that performs DXA should determine the precision of its scans from a patient sample that represents the usual subjects of that facility, for example a clinic that performs DXA scans predominantly on elderly subjects should determine precision based on a reference sample of elderly subjects (Blank et al 2006)(diagnostic evidence level IV).

Another study addressing the applicability of DXA for vertebral assessment in specific patient subgroups looked at its ability to detect fractures in Type 2 diabetic women. The study involved 716 women with diabetes and 150 control women. Both groups were assessed using standard thoracic and lumbar radiography as well as DXA. Diabetic patients exhibited a fracture prevalence of 22.1 per cent (158 subjects) and the control subjects had a prevalence of 17.3 per cent (26 subjects). Despite the similar (i.e. not significantly different) levels of fracture prevalence, diabetic women had higher lumbar BMD (L-BMD). L-BMD was not associated with fractures in diabetic women but contrastingly was associated with fractures in the control women. The authors concluded that for diabetic women DXA for fracture detection was not sensitive enough to assess fractures in these women and that the diabetic subject's bone quality was not associated with BMD (Yamamoto et al 2007)(level III-2 diagnostic evidence).

Osteoporosis is more common in women than in men and the majority of data for DXA vertebral assessment comes from studies of women. Vallarta et al investigated vertebral fracture assessment (VFA) in men using BMD determined by DXA (Vallarta-Ast et al 2007) (diagnostic evidence level IV). DXA was used to assess 1,168 men with VFA. These subjects were referred to the DXA centre due to clinical indications requiring BMD assessment. VFA using DXA was adequately assessed in 78 per cent of T4-L5 and 93 per cent of T8-L5 vertebrae. Vertebral fractures were found in 32 per cent of men assessed. Of men with no history of vertebral fracture, 17 per cent were found to have vertebral fractures in this population. It was found that the prevalence of vertebral fracture was increased in subjects with height loss of ≥ 6.4 cm. This, and low BMD by DXA were recommended to be used as indications for referring subjects for VFA.

In a study of 85 high-risk subjects a DXA based morphometry scan was conducted at the same time as DXA BMD assessment and compared to standard radiography for the detection of vertebral fractures. Upper thoracic vertebrae were difficult to assess due to poor image quality in this area, a known limitation of DXA and radiography. Greater than 50 and 10 percent of vertebrae at the T4 and T5 level were not able to be assessed by DXA morphometry and radiography respectively. The sensitivity of DXA for detecting all fractures was 69 per cent and specificity was 74 per cent. If only more severe, i.e. more obvious and easy to detect, fractures (grades 2 and 3) were used to assess DXA performance, as expected, sensitivity and specificity rose. The authors qualify the moderate success of DXA morphometry by noting the per-vertebra negative predictive value is always above 85 per cent. In addition the accuracy of DXA morphometry is highest where vertebral fractures are highest, and therefore DXA may be a useful screening tool for *ruling out* subjects being assessed for vertebral fractures. The remainder could be assessed by radiography for more accurate fracture detection (Chapurlat et al 2006)(level III-2 diagnostic evidence).

Another study compared DXA to standard thoracic and lumbar radiography (Damiano et al 2006). It was reported that in the subject group, 136 post-menopausal women, that 61 patients (45%) had at least one vertebral fracture. Vertebrae that were unable to be adequately assessed were higher in DXA (12.4%) versus radiography (1%). Using an algorithm they designed, the authors reported that they could reduce the number of subjects undergoing standard radiography by 32 per cent by using DXA (level III-2 diagnostic evidence).

As practiced, DXA BMD and VFA are reported to be relatively accurate clinical tests. Despite the shortcomings, such as inability to assess some vertebrae and poor results in some subject groups, DXA compares favourably with standard radiography. For maximal clinical accuracy DXA should be, and to a great extent is, used only on populations with a high prevalence of fractures or low BMD.

AUGUST 2007 OTHER ISSUES:

One of the issues surrounding DXA assessment of vertebral fractures is the manual exclusion of vertebral artifacts. This is usually performed by an expert physician. A study comparing a software solution to perform this function to expert physicians found that the software performed equally as well as the physicians when predicting vertebral fractures were used as the marker for success (Tsang & Leslie 2007).

In a strongly worded exposition, Bolotin reviews evidence against the current practice of measuring BMD by DXA. The author states “in vivo bone density methodology is inherently flawed, giving rise to substantial systematic inaccuracies that are fully consistent with being causal to virtually all those anomalies, inconsistencies, and self-contradictions which beset the field of bone fragility.”

This review repudates the current standard practice of using DXA to measure BMD for reasons such as: the unproven transfer of theory founded on laboratory-based bone density measurements by DXA (e.g. on ashed bone samples) to clinical practice. The author states that the measurement of bone density by DXA *in vivo* is impossible according to the established principles of physics, i.e. the *in vivo* target of DXA BMD measurements contain more than the limit of two X-ray absorptiometrically disparate substrates dictated by the “two component” DXA limitation. As clinically measured *in vivo* DXA BMD assessments inherently involve sampling more than two substrates (e.g. bone, muscle, fat, marrow) Bolotin claims that BMD as determined by DXA is a misnomer and that within a single patient variation of various factors, such as marrow volume, may result in the subject being misclassified as either normal or osteoporotic despite the contrary being true (Bolotin 2007).

AUGUST 2007 COST IMPACT :

No information was found regarding cost impact in the evidence reviewed in this summary.

AUGUST 2007 SUMMARY OF FINDINGS

Although DXA for BMD and fracture diagnosis is widely practised and, indeed most of the studies reviewed in this summary indicate a positive stance toward DXA VFA, a recent review of the fundamental theoretical basis of using DXA for BMD, argued strongly that BMD as determined by DXA was inherently and un-correctably flawed and was not actually measuring BMD. In addition, no evidence was identified indicating the cost effectiveness of DXA for VFA.

AUGUST 2007 HEALTHPACT ACTION

Bone mineral density testing represents a large portion of health care budgets and testing is widespread. Data supporting the use of DEXA for BMD testing is getting weaker rather than stronger and ultrasound may be a more accurate way to measure BMD. Therefore HealthPACT have recommended that a Prioritising Summary on the use of ultrasound to measure BMD be written.

NUMBER OF STUDIES INCLUDED

Total number of studies	
Level III-2 evidence	3
Level IV evidence	2

AUGUST 2007 REFERENCES:

Arabi, A., Baddoura, R. et al (2007). 'Discriminative ability of dual-energy X-ray absorptiometry site selection in identifying patients with osteoporotic fractures', *Bone*, 40 (4), 1060-1065.

Blank, R. D., Malone, D. G. et al (2006). 'Patient variables impact lumbar spine dual energy X-ray absorptiometry precision', *Osteoporos Int*, 17 (5), 768-774.

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Damiano, J., Kolta, S. et al (2006). 'Diagnosis of vertebral fractures by vertebral fracture assessment', *J Clin Densitom*, 9 (1), 66-71.

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Nicholson, P. H. & Alkalay, R. (2007). 'Quantitative ultrasound predicts bone mineral density and failure load in human lumbar vertebrae', *Clin Biomech (Bristol, Avon)*, 22 (6), 623-629.

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Vallarta-Ast, N., Krueger, D. et al (2007). 'An evaluation of densitometric vertebral fracture assessment in men', *Osteoporos Int*.

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AUGUST 2007 SOURCES OF FURTHER INFORMATION:

No sources were identified.