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Mini Review

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Dual Energy X-Ray Absorptiometry: Beyond Bone Mineral Density

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Introduction

This paper provides an overview of the presentation at the Nuclear Medicine and Radiation Therapy conference in July 2016.

The internationally agreed definition of osteoporosis is "a progressive systemic skeletal disease characterised by low bone mass and micro architectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture" [1]. While the modern definition of osteoporosis has only been adopted for a relatively short period of time, the concept of osteoporosis has been noted throughout history, with Hippocrates in 500BC writing "the vertebrae of the spine when contracted into a hump behind from disease" [2] and more recently, Cooper [3] noting that old age is readily detected in the skeleton, bones become thin in their shell and spongy in their texture. However, it is only twenty-one years ago that dual-energy x-ray absorptiometry (DXA) has become the gold standard for the diagnosis of osteoporosis, with an internationally agreed diagnostic criteria [4,5].

One in two women and one in five men over the age of 50 in the UK will fracture a bone, often as a result of osteoporosis [6], with fragility fractures occurring primarily, but not exclusively, at the distal radius, vertebrae and hip [6]. It is currently estimated that 21 million men and 137 million women worldwide are at a high probability of fracture and this is estimated to double over the next 40 years [7].

Dual Energy X-Ray Absorptiometry

Dual energy x-ray absorptiometry is commonly considered to be the gold standard for the diagnosis of osteoporosis and it is supported by the widest evidence-base and clinical utilisation [5,8]. Radiographs are an insensitive method to accurately quantify bone mineral density (BMD) changes and require a 30 percent to 50 percent loss of BMD before changes become apparent [9]. Dual energy x-ray absorptiometry provides an aerial measurement of bone mineral, yielding a measurement in g/cm^2. However, this absolute value is difficult to interpret without the use of normative reference data for comparison. Therefore T- and Z-scores are created from equations using the mean and standard deviations of the reference data. A T-score compares the value to a young-adult population and a Z-score provides an age-matched comparison. Both T- and Z-scores tend to be gender and ethnicity specific, but there is widespread deliberation about the most appropriate comparisons for men and non-caucasian patients at present. Using T-scores enables a diagnosis to be made using the WHO criteria [4] for the diagnosis of osteoporosis. A T-score of >-1.0 is considered normal, ≤ -1.0 to -2.5 is considered as osteopenia and ≤ -2.5 is considered to indicate osteoporosis [4].

However, DXA is not without its limitations, both in the diagnosis of osteoporosis and in the monitoring of disease progression or therapeutic intervention [10]. Patients diagnosed with osteoporosis using DXA do not all go on to fracture, whereas conversely the majority of fractures occur in women diagnosed with osteopenia (low bone mass) or normal by BMD criteria [11]. The potential for spurious results or uninterpretable scans to lead to inappropriate management advice is a frequent problem (Figure 1) [12]. There are many confounding variables which artificially elevate BMD, particularly in the lumbar spine including: degenerative changes, aortic calcification and vertebral fractures. These tend to be more prolific in the elderly and must be taken into account when interpreting scans. Furthermore, incorrect DXA scanning technique and the presence of artefacts can lead to misinterpretation, which can result in treatment mistakes [13]. The precision errors within DXA are also a major factor when considering changes in BMD when monitoring disease progression or responses to therapeutic intervention. The average quoted precision errors in DXA are similar to the annual bone loss in an elderly population and therefore care needs to be taken when interpreting longitudinal DXA scans [14]. The scan intervals need to be on average 2 years apart, except in cases where potent drugs with deleterious effects on bone, or potent therapies, such as parathyroid hormone are being taken [15]. Furthermore, precision errors have been demonstrated to increase with increasing obesity and therefore consideration of patient size needs to be taken into account when interpreting longitudinal results [14].

Clinical Risk Factors

Due to the uncertainties related to DXA scans, other methods have been developed to improve its fracture prediction, with the new WHO clinical risk factors tool "FRAX" becoming widely adopted [8]. This tool enables the 10 year probability of fracture to be calculated both without and with the addition of hip BMD. Patients referred for a DXA scan can be identified through identifying those with clinical risk factors, including age, a low body mass index, fracture history, maternal or paternal hip fracture, current smokers, glucocorticoid use for >3 months (>5 mg/day), rheumatoid arthritis, alcohol intake >3 units/day, secondary osteoporosis (resulting from drugs and diseases known to affect bone metabolism and hypogonadism including a menopause <45 years of age) [8]. Referral criteria should be set by individual services and align with national guidelines. The evidence-base demonstrates that fracture prediction is improved with the use of both BMD and clinical risk factors [16], thus enabling better targeting of therapeutic interventions.

Vertebral Fracture Assessment

The use of vertebral fracture assessment (VFA) using DXA scanners can further reduce the uncertainties associated with DXA-based BMD measurements (Figure 2). Patients who have a vertebral fracture are more likely to have further vertebral fractures and are more likely to suffer a hip fracture. One in five women with an incident vertebral fracture will suffer a further vertebral fracture within a year [17]. Furthermore, the risk of incident vertebral fractures increases with the

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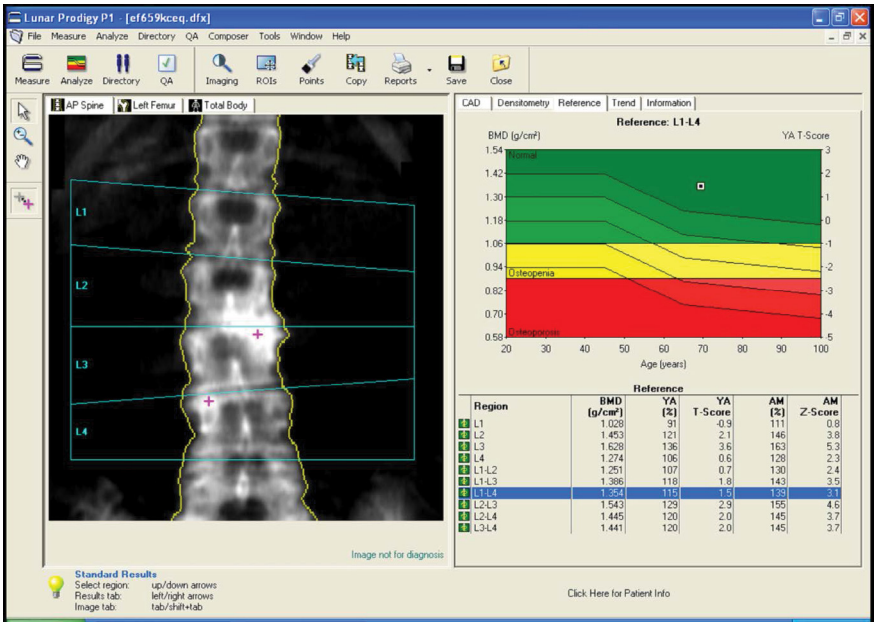

Figure 1: An un-interpretable DXA scan of the lumbar spine due to wide spread degenerative changes artificially elevating the BMD. A diagnosis cannot me made from L1 alone, the only remaining vertebrae within the region of interest which is seemingly normal on this image.

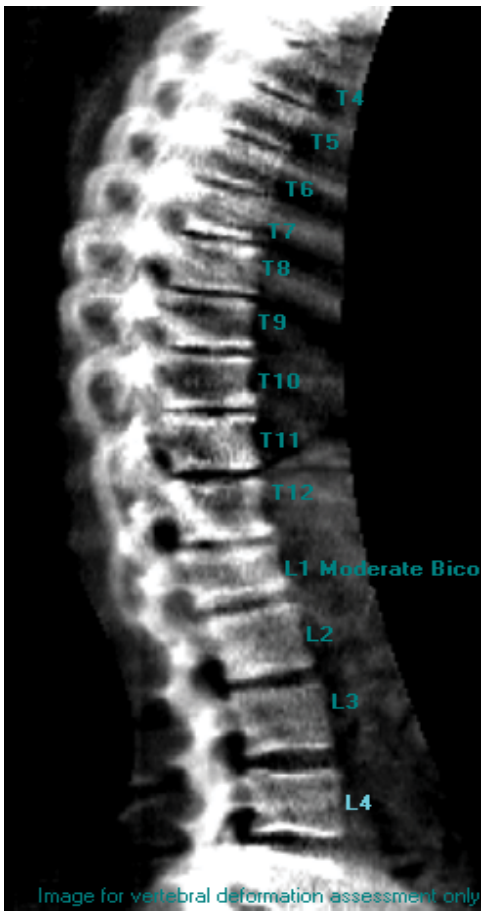

Figure 2: Vertebral fracture assessment (VFA) using DXA and morphometry to assist in the quantification of fracture type and severity.

number of prevalent vertebral fractures, with the relative risk increasing from 3.2 to 23.3 for one to three or more prevalent vertebral fractures respectively [18]. These risks can be mitigated through treatment. For example, a 65 year old female with one vertebral fracture has a 25% chance of sustaining a further fracture within five years but this can be reduced by half with bone-sparing therapies [19]. However, not all fractures will come to clinical attention and therefore methods are required to identify those with sub-clinical and missed vertebral fractures [20]. DXA affords a low dose opportunity to detect sub-clinical and missed vertebral fractures. On the spectrum of radiation doses used in clinical imaging, DXA and VFA result in very small doses in the microsievert range and by definition these doses are considered to be "trivial" [21,22]. However, under the ionising radiation (medical exposure) regulations (IR(ME)R), all radiation exposures in patients for medical reasons must be justified [23]. Therefore, undertaking VFA in a population who are at a low risk of vertebral fracture and without a level of clinical suspicion of a fracture is inappropriate and in breach of IR(ME)R. However, in a high risk population, it is acceptable to undertake a VFA even without clinical suspicion in an individual, based on their risk profile and probability that they may have a fracture. Schousboe et al. suggest it is likely to be cost effective and appropriate to undertake a VFA on all Caucasian women over the age of 70 with a low BMD, [24]. However, each scan adds extra time and financial costs to the overall examination and for reporting of the VFA scans. In addition to the financial burden, it is important to consider the added radiation dose associated with VFA and ensure patients scanned are appropriately selected. The International Society for Clinical Densitometry (ISCD) has published recommendations for the selection of patients VFA, though some UK hospitals have more simplified models [25,26]. The ISCD do not suggest the need for further radiographic imaging to characterise a fracture identified using VFA. However, in the UK many clinicians would recommend characterising an incident vertebral fracture with a radiograph or other imaging (as indicated), since VFA cannot discriminate between osteoporosis-related fractures and those resulting from other causes, such as malignancy [27].

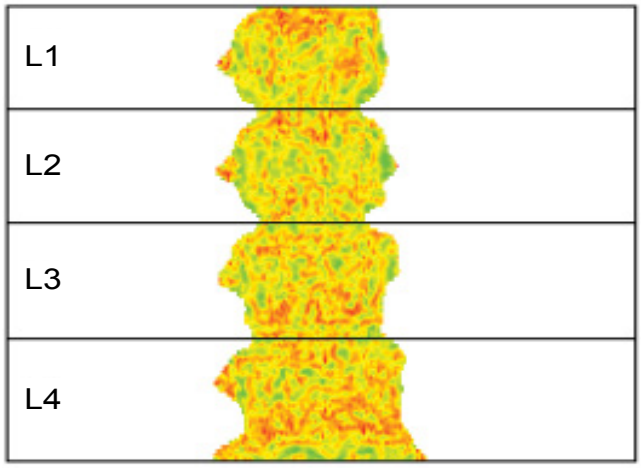

Figure 3: Trabecular bone score.

Trabecular Bone Score

While DXA has typically only provided BMD and bone area information, it is known that this only accounts for approximately 50% of bone breaking strength [28] and bone geometry and microstructure also play an important role [29]. The trabecular bone score (TBS) has been developed to provide a measurement of trabecular structure in the spine from the DXA scan (Figure 3) and this has been demonstrated to have a low precision error in line with that seen for DXA [30]. It has also been demonstrated to predict fracture independently of BMD, which affords the opportunity to increase fracture discrimination by combining the techniques [31,32]. Trabecular bone score is supported by an increasing evidence-base and has clear potential for the future.

Total Body Scans

There has been increasing interest from the elite athlete population in using total body (TB) DXA scans as a means of measuring body composition. Total body scans are acquired using the same low-dose technology as BMD scans and provide total body and compartmentalised bone, lean tissue and fat mass measurements [33]. Dual energy x-ray absorptiometry nonetheless, does not afford the perfect tool for the measurement of body composition. Precision errors have been demonstrated to vary between individuals due to biological variations, such as different body mass indexes, body fatness and tissue inhomogeneity [34]. The precision errors of DXA measurements are important for characterising the ability to detect longitudinal changes [35] and clinically, minimum time frames are used based on the likely rate of change in a patient's BMD compared to the precision error expected from the scanner and skeletal sites used.

Changes in fat or lean tissue may be of interest in some clinical groups [36] and in elite athletes [37], particularly in decision making about their potential injury risk. Therefore, one off measurements in athletes may be useful for characterising their body composition. However, there is currently a poor evidence-base for the repeated use of TB DXA in the athlete population. The ability of TB DXA to accurately and precisely measure BMD, fat and lean tissue within populations of differing muscle and fat mass is unlikely to be comparable [38] and a previous study demonstrated larger precision errors in spine, hip and total body in obese groups [14,39]. Furthermore, measurements in athletes are confounded due to water retention in skeletal muscle post training, with acute increases in muscle water content being demonstrated post strenuous resistance training [40,41]. Therefore scanning athletes using DXA to measure body composition requires consideration of the duration since their last training session to prevent adding further errors to the measurements. As stated by Haroon [42] "If precision errors in detecting body composition changes over time are not avoided, it is likely that results will get misinterpreted or possibly used inappropriately, leading to miserable consequences".

Dual energy x-ray absorptiometry sports performance assessment (DSPA) is not a medical exposure and is not currently a justified practice. Any exposure in an athlete that can be deemed as a medical exposure, such as for rehabilitation, is regulated by the Ionising Radiation (Medical Exposure) Regulations 2000. A more robust evidence-base is required before the scanning of athletes can be considered as a justified exposure under the Justification of Practices Involving Ionising Radiation Regulations 2004.

In conclusion, while BMD measurement by DXA is currently the gold standard for the assessment of osteoporosis, there are still many uncertainties in diagnoses using this technology. Combining DXA with clinical risk factors can improve fracture prediction, while VFA scans in high risk patients can further improve targeting therapies by detecting often sub-clinical or missed vertebral fractures. Trabecular bone score based on lumbar spine DXA scans has been demonstrated to independently discriminate fracture, so is a promising addition to DXA scans for the future. Finally, TB DXA scans can provide body composition measurements as well as bone density information and these are of interest to the elite athlete population, but this practice is currently not justified in the United Kingdom.

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