R E V I E W

A review of the use of dual-energy X-ray absorptiometry (DXA) in rheumatology

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Abstract: The principal use of dual-energy X-ray absorptiometry (DXA) is to diagnose and monitor osteoporosis and therefore reduce fracture risk, associated morbidity, and mortality. In the field of rheumatology, DXA is an essential component of patient care because of both rheumatologists' prescription of glucocorticoid treatment as well as the effects of rheumatological diseases on bone health. This review will summarize the use of DXA in the field of rheumatology, including the concern for glucocorticoid-induced osteoporosis, as well as the association of osteoporosis with a sampling of such rheumatologic conditions as rheumatoid arthritis (RA), systemic lupus erythematosus, ankylosing spondylitis, juvenile idiopathic arthritis, and scleroderma or systemic sclerosis. Medicare guidelines recognize the need to perform DXA studies in patients treated with glucocorticoids, and the World Health Organization FRAX tool uses data from DXA as well as the independent risk factors of RA and glucocorticoid use to predict fracture risk. However, patient access to DXA measurement in the US is in jeopardy as a result of reimbursement restrictions. DXA technology can simultaneously be used to discover vertebral fractures with vertebral fracture assessment and provide patients with a rapid, convenient, and low-radiation opportunity to clarify future fracture and comorbidity risks. An emerging use of DXA technology is the analysis of body composition of RA patients and thus the recognition of "rheumatoid cachexia," in which patients are noted to have a worse prognosis even when the RA appears well controlled. Therefore, the use of DXA in rheumatology is an important tool for detecting osteoporosis, reducing fracture risk and unfavorable outcomes in rheumatological conditions. The widespread use of glucocorticoids and the underlying inflammatory conditions create a need for assessment with DXA. There are complications of conditions found in rheumatology that could be prevented with more widespread patient access to DXA.

Keywords: dual-energy X-ray absorptiometry, FRAX, osteoporosis, rheumatology, vertebral fracture assessment, body composition

Introduction

Dual-energy X-ray absorptiometry (DXA) is a noninvasive quantitative bone density–measurement technique most commonly used to diagnose osteoporosis. DXA is frequently used in rheumatology because rheumatologists commonly use glucocorticoid (GC) treatment for a variety of conditions, and GCs are known to cause bone loss and an increased risk of fractures.[1] In addition, the increase in inflammatory cytokines in various rheumatologic conditions can result in bone loss and increased rates of fractures. The increase in fractures seen in these conditions may be due to other features of the disease and independent of bone loss.[2,3]

Therefore, the practice of rheumatology involves monitoring bone health with DXA, both because of the side effects of the treatments and because of the

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underlying conditions. In this paper, the authors have reviewed clinical literature related to DXA and the specific rheumatology conditions discussed, published between 1989 and 2012, using a search of Medline, with particular attention to the important English-language bone and specialty journals as well as the published position statements of the International Society for Clinical Densitometry (ISCD).

The development of applications, policies, and regulations for using DXA, including FRAX

The US Food and Drug Administration approved DXA for clinical use in 1988, and the Scientific Advisory Board of the National Osteoporosis Foundation (NOF) proposed four clinical conditions for measuring bone-mineral density (BMD) to the US Health Care Financing Administration.[4]

The four conditions in which the measurement of BMD was thought to have clinical significance included: (1) estrogen-deficient women, (2) patients with vertebral abnormalities or roentgenographic osteopenia, (3) patients receiving long-term GC therapy, and (4) patients with asymptomatic primary hyperparathyroidism. In 1998, these four recommendations were incorporated into the original US Medicare guidelines for bone-density measurement and reimbursement with the Bone Mass Measurement Act, thereby codifying concern about GC-induced osteoporosis at the onset.[5,6]

The World Health Organization (WHO) also used DXA-based BMD measurement when it issued a definition of osteoporosis in 1994 that included an osteoporosis diagnosis based on BMD criteria. Using a reference mean of BMD from a young, healthy population, the WHO defines osteoporosis in postmenopausal Caucasian women when the BMD at the spine, hip, or wrist is 2.5 or more standard deviations below the reference mean, or a T-score of −2.5 or less.[7] In addition, the WHO included the clinical definition of osteoporosis based on the presence of a fragility fracture.

In 2008, with further refinement of the clinical application of BMD measurement, the WHO released an online tool for fracture risk assessment called FRAX.[8] This tool uses selected clinical information as well as femoral neck BMD to predict the 10-year probability of a major osteoporotic fracture and a hip fracture in an individual. It was developed by the WHO Collaborating Centre for Metabolic Bone Diseases, University of Sheffield, UK, in collaboration with other scientific societies and is based on specific country data for fracture and death rates for women and men over the age of 40 years. The goal of the FRAX tool is to help clinicians better select patients for fracture-prevention treatment and

thus improve "the allocation of scarce healthcare resources for patients most likely to benefit from treatment."[9]

DXA BMD measurements are needed to select patients for osteoporosis treatment. In the US, the 2008 NOF treatment guidelines rely on DXA BMD data for treatment thresholds.[10,11] The NOF guidelines incorporated the FRAX model to recommend treatment in those patients with osteopenia who had a 10-year risk for hip fracture of >3% or for a composite of fractures (hip, spine, humerus, wrist) of >20%. The implication was that those who were below these cutoff points were generally at lower risk and pharmacologic therapy might be withheld.

Although there are other methods for the measurement of BMD, DXA is the only technology for classifying BMD according to the WHO established criteria and the only technology that is validated for BMD input with the WHO FRAX fracture risk–assessment algorithm. Quantitative ultrasound (QUS) of the heel, as measured by broadband ultrasound attenuation and speed of sound has been proven to predict hip fractures and all osteoporotic fractures in elderly women as well as DXA.[12,13] QUS can help identify patients who have a high risk of osteoporotic fracture and therefore those who would benefit from treatment, or conversely those patients with a low risk of fracture who do not require medical investigation. However, QUS has not been concluded to be valuable in monitoring response to treatment.

As a result of the widespread use of FRAX, various concerns have arisen regarding the selection of clinical information for the tool and the possibility of overestimating or underestimating the fracture risk in individual cases. In response, the ISCD in collaboration with the International Osteoporosis Foundation (IOF) convened a Position Development Conference (PDC) in Bucharest, Romania in 2010.[9] The summary of the work of the conference provides a "… distillation of current knowledge in the discipline of bone densitometry," clarification about the clinical elements in FRAX, and direction for future scientific research.[9]

There are other fracture risk–prediction tools besides FRAX that rely on BMD from DXA. For example, the Garvan Fracture Risk Calculator was developed using data collected in the Dubbo Osteoporosis Epidemiology Study conducted by the Bone and Mineral Research Program of Sydney, Australia's Garvan Institute of Medical Research and uses four clinical risk factors and BMD from DXA.[14] Also the "lower limit of normal" method uses a single DXA BMD measurement to predict fractures in select populations and may be more useful than T-scores.[15,16]

Despite the growing importance of DXA in clinical practice, there is alarming concern about patent access to this technology. In the US, severe reductions in Medicare reimbursement to levels far below the cost of providing the procedure have resulted in the closing of some DXA facilities.[17–21] Decreased access to DXA facilities results in fewer patients being diagnosed with osteoporosis, fewer patients treated to reduce fracture risk, more fractures, more complications, and higher health-care costs.

Glucocorticoids and osteoporosis

GCs have been recognized in rheumatology as the most common cause of drug-related osteoporosis, and early guidelines for DXA in rheumatology included the use of these compounds as a reason to perform DXA bone-density measurement.[22] As noted previously, Medicare guidelines (and other subsequent guidelines) have included GC treatment as a reason to perform DXA testing, and the Medicare justification benchmark dose is the equivalent of prednisone 5 mg/day for 90 days or more.[5,12,23–27] As a result of the rapid bone loss and increased fracture risk soon after initiation of GC treatment, Medicare guidelines include a provision for frequent (every 6 months) DXA monitoring of these patients, although most management guidelines call for yearly monitoring.[28]

Osteoporosis has been estimated to occur in up to 50% of patients who have received GCs for 6 months or more and perhaps one-third to one-half of long-term GC users develop fractures.[29] The multiple mechanisms of bone loss from the use of GCs include inhibition of calcium absorption from the gastrointestinal tract, decreased renal tubular calcium reabsorption, reduced gonadotrophin and growth-hormone release, vitamin D deficiency, depletion and inhibition of osteoblasts and osteocytes and increased osteoclastic activity, and bone resorption.[30,31]

The increased fracture risk with GC users has been shown to be approximately one standard deviation higher than the risk in the general population.[32] Furthermore, data from asthma patients treated with GCs indicate that GC-associated fractures occur at a higher BMD than in those not receiving glucocorticoids.[33]

The occurrence of fractures in GC patients at higher-than-expected BMD may be explained by risk factors that are independent of BMD but related to GC use. These fracture risks in GC-treated patients that are independent of a decline in BMD include increased risk of falling, muscle weakness and frailty, and changes in bone material properties that are not captured by BMD measurements.[19,34] Fracture risk has also been correlated with daily and cumulative GC dose.[35]

Therefore, it is not surprising that the WHO FRAX tool includes GC use as a clinical risk factor to be included in the calculation of a 10-year fracture-risk estimate.[8] However, as with the case of rheumatoid arthritis (RA) as a risk factor in FRAX, the GC question is a binary variable and does not take into account dose and duration of treatment. The ISCD-IOF PDC in Bucharest addressed this issue and noted that higher dose, longer duration, and inhaled GC use increases the fracture risk in a way that is not captured in the FRAX calculation.[36] Thus FRAX may underestimate fracture risks in certain situations of GC treatment.[37]

Rheumatoid arthritis

Patients with rheumatoid arthritis (RA) have been shown to incur bone loss and hip and spine fractures at a higher rate than control populations, and RA has been included in FRAX as a clinical risk factor independent of BMD.[38–50] RA is unique among the clinical risk factors included in the WHO FRAX tool. It is the only secondary cause of osteoporosis that is considered independent of BMD in the WHO FRAX fracture-risk algorithm.[3]

RA is considered a binary risk factor in FRAX (either present or absent), yet it is a systemic inflammatory disease that varies in disease activity from mild to severe. The assumption that more severe or active RA would be associated with more severe osteoporosis has not been borne out in all studies. Certain RA disease parameters such as disease activity score and measurement of acute-phase reactants have been correlated with decreased bone density but not necessarily an increased fracture risk. While other parameters such as disease duration, functional class, and Health Assessment Questionnaire results have been associated with an increased fracture risk as well as decreased bone density.[2,38,39,41,42,51,52]

There are other reasons in addition to inflammation that may contribute to the association of RA with osteoporosis and fragility fractures, including the use of GCs, Disease-modifying antirheumatic drugs, inactivity, and increased risk of falling.[38,53–59] The relative contribution of these factors to the development of osteoporosis and osteoporotic fractures in these patients is not well understood. Apart from the use of GCs, there is not enough evidence to associate specific RA medications and fracture risk. In some cases, the data are conflicting, and in the case of anti–tissue necrosis factor (TNF) agents, there is information from the CORRONA database that indicates that these agents can be protective of fractures.[59]

There are other rheumatology conditions that are noted to be causes for secondary osteoporosis and fractures,

and these causes, as with RA, can be multifactorial, including the effect of the disease on decreasing bone density, the increased risk of falling, and medications used to treat the conditions, including GCs.[22,23]

Lupus

Systemic lupus erythematosus (SLE) is a chronic inflammatory disease primarily affecting women in their childbearing years and characterized by autoreactive immune dysregulation. Symptomatic fractures in women with lupus occur at five times the rate of similarly aged healthy women without lupus.[60] Multiple studies have demonstrated significantly lower BMD and higher rates of osteoporosis in SLE patients relative to age-matched controls, and prevalence of osteoporosis in cross-sectional studies has ranged from 1.4% to 68%.[61]

Lupus-associated low bone density and osteoporosis increase is multifactorial, involving both disease and patient-related factors.[61] The traditional risk factors for osteoporosis play a key role in SLE patients since most are female; therefore, a priori, at higher risk. In addition, as treatment of SLE improves, more women are living longer with the disease, placing them at a higher risk of bone loss as they age. The symptoms of SLE include fatigue, arthralgia, and arthritis, which may lead to decreased physical activity, itself a risk factor for osteoporosis. Patients with SLE must often avoid significant sun exposure or risk disease flare or exacerbation of photosensitive rashes. This avoidance of ultraviolet B radiation from the sun can lead to reduced levels of vitamin D, which has been reported to cause reduced BMD in SLE patients.[62]

Although GCs are often used to treat SLE, not all investigators agree on the importance of this medication as a risk factor for osteoporosis in SLE.[62,63] Other medications sometimes used in the treatment of SLE also may contribute to alterations in bone metabolism, such as methotrexate or cyclosporine and interestingly hydroxychloroquine may have a protective effect.[64]

As in other rheumatic diseases, increased levels of inflammatory cytokines such as interleukin-1, interleukin-6, and tumor necrosis factor-alpha cause increased osteoclastogenesis and activity, thereby contributing to loss of bone density. Higher levels of these cytokines are seen in SLE. This in turn likely contributes to osteopenia and osteoporosis. Some studies have described alterations in bone metabolism and sex hormones levels in SLE patients. Redlich et al noted significantly reduced levels of osteocalcin, a marker of bone formation, and reduced levels of serum testosterone.[65] While there appears to be a correlation between decreased BMD and accumulated organ damage in SLE, disease activity in and of itself does not appear to be a major risk factor.[61]

Ankylosing spondylitis

Ankylosing spondylitis (AS) is a rheumatic disease characterized by enthesitis, axial skeletal inflammation, and sacroiliitis. In contrast to the bony erosions seen in RA, AS is a disease of new bone growth. This leads to spinal ankylosis and calcific enthesopathy. Despite this tendency for new bone production, patients with AS also develop decreased BMD and osteoporosis. Many traditional risk factors for osteoporosis do not play a significant role in AS. Unlike patients with RA or SLE, who are typically older and female, patients with AS are younger and more often male. In addition, while GCs are a common therapy in RA and SLE, they are rarely used in AS.

The dichotomous nature of bone metabolism in AS may be best explained by the uncoupling of osteoblast-mediated local bony growth from osteoclast-mediated resorption of bone. As a systemic inflammatory disease, AS is characterized by elevated proinflammatory cytokines that drive the production of the receptor activator of nuclear factor kappa B ligand (RANKL).[66] This increase in RANKL stimulates the differentiation and activation of osteoclasts, leading to loss of bone mass globally. At the same time, local inflammation seems to lead to local accretion of bone, possibly through bone morphogenetic proteins and wingless-type like (Wnt) signaling.[67] Suppression of inflammation with anti-TNF therapy has been shown to improve symptoms as well as reverse BMD loss, presumably by attenuating the proinflammatory cytokine cascade.[68]

Despite the younger population and relatively early onset of disease, osteoporosis is not an uncommon finding in AS. Reported prevalence has ranged from 4.3% to 62%, the wide variance likely a result of differing patient populations, technique in measuring BMD, and site chosen to assess BMD.[69,70] AS is a disease of bony overgrowth in the axial skeleton, thus a DXA scan of the lumbar spine may overestimate BMD because of progression of syndesmophyte formation. This density artifact has been confirmed by studies showing increasing lumbar BMD and decreased femoral BMD in longstanding disease.[71] Other investigators, however, have found that BMD assessment at the lumbar spine is, in fact, more sensitive than that done at the femoral neck and that the presence of bridging syndesmophytes did not raise lumbar BMD until advanced bony growth had occurred.[69] In contrast, femoral neck BMD has been shown to reliably decrease with longer disease duration.

Some studies have shown that risk of osteoporosis correlates with disease severity, but this association has not been confirmed universally. Low body mass index has been identified as an additional risk factor.[72]

AS patients have a fivefold-higher risk for vertebral compression fractures than unaffected controls, and many of these fractures may go undiagnosed clinically.[73] Ghozlani et al found that most fractures occurred in the midthoracic spine or the thoracolumbar junction.[72] Vertebral fractures can cause significant morbidity in patients with AS and may occur with minimal trauma. Patients with AS do not appear to be at higher risk from fractures at other sites.[74]

Juvenile idiopathic arthritis

Juvenile idiopathic arthritides (JIA) represent a spectrum of rheumatologic diseases in children characterized by varying numbers and distribution of affected joints as well as differing extra-articular manifestations. The etiology of BMD loss in these diseases likely parallels that in adult RA, ie, systemic inflammation ultimately leading to increased osteoclast activity and number. Assessing JIA patients for osteoporosis or osteopenia is complicated by the variable physiologic state of the pediatric skeleton. BMD or bone-mineral content must be compared to age-matched norms (Z-scores), and the use of T-scores is invalid since comparing an undeveloped and maturing skeleton to that of a young adult would lead to underestimation of BMD.[75] There is also little data to correlate fracture risk and BMD in this population.[76] DXA is useful in the pediatric population, but body size must be accounted for when interpreting results.[77]

Despite the complications in assessing BMD in this population and the heterogeneity of the JIA subtypes, these patients have been consistently shown to have lower BMD than healthy age-matched controls and to be at further risk of decreased BMD into young adulthood.[78–80] Risk factors for diminished BMD include disease severity and JIA subtype, with polyarticular disease in particular associated with reduced BMD in the hip.[78]

A small study of young females with JIA noted those with delayed menarche had Z-scores that were significantly decreased when compared to the normal population and JIA disease activity correlated with menarche delay.[81]

As in adults, an association between GC use and loss of BMD has been demonstrated as well. In one early study of 46 patients, 23 developed vertebral fractures, and all fractures occurred after reaching a cumulative prednisone dose of 5 g.[82]

Systemic sclerosis

Scleroderma or systemic sclerosis (SSc) is female-predominant connective tissue disease that causes fibrosis of the skin and internal organs and has been associated with an apparent decrease in BMD.[83–90] There are two clinical subtypes, diffuse cutaneous SSc (dcSSc) and limited cutaneous SSc (lcSSc), which have differing courses but with considerable overlap, and all SSc patients are at risk of developing serious organ involvement. Furthermore, several authors have reported no differences in the finding of low BMD between dcSSc and lcSSc subtypes.[89,91,92]

The prevalence of osteoporosis in SSc (~25%) appears to be similar to that seen in RA, but DXA testing occurs less often in SSc patients and the BMD appears to be lower than in RA controls.[91] Various explanations for the finding of osteoporosis in SSc patients have been put forth, including chronic inflammation, inactivity, malabsorption, renal insufficiency, medications such as GCs, and even skeletal calcium mobilization as part of the subcutaneous calcinosis process, but the studies are small and involve heterogeneous SSc populations.[91,93,94]

Furthermore, vitamin D deficiency was noted to be quite prevalent (81%) in one study of SSc patients but patients with vitamin D deficiency did not demonstrate lower BMD.[93] Other efforts to correlate clinical parameters of SSc with BMD have produced inconsistent results, including disease duration, body mass index, early menopause, age, and internal organ involvement, again related to the small study sizes and heterogeneous populations.[85,87–91] As a result, some authors have suggested that SSc itself is a risk factor for osteoporosis.[85,88]

Other uses of DXA
Vertebral fracture assessment

Vertebral fractures are often clinically unrecognized, but are an important predictor of future fractures or poor health.[95] Despite the absence of clinical recognition, these fractures are associated with a decline in pulmonary function, challenges with activities of daily living, and early death.[96–99] Furthermore, a vertebral fracture indicates an increased risk of future osteoporotic spine and hip fractures, independent of age and BMD.[100]

An additional feature of most DXA equipment is to be able to capture lateral spine images, which can demonstrate vertebral deformities in a process known as vertebral fracture assessment (VFA). Although there are limitations above the T8 vertebral body, fractures found with VFA correlate well with conventional lateral spine radiographs.[101–103] Optimal performance of VFA requires training and adherence

to quality standards, which can be found at the ISCD website – http://www.iscd.org.[17]

Rheumatoid arthritis has been noted to be a risk factor for vertebral fractures, and the presence of vertebral fractures is inversely related to the use of disease-modifying anti-rheumatic drugs and GCs.[104] VFA can therefore be an important application of DXA in rheumatology.

Therefore, performing VFA at the same time of DXA BMD measurement can provide patients with a rapid, lower-cost, convenient, and low-radiation-exposure opportunity to detect vertebral fractures. Detection of these fractures can, in turn, change diagnostic classification, assessment of fracture risk, and treatment decisions.[105]

Body composition

DXA has become a reliable and established technique for analyzing the composition of body soft tissue and measuring that which is fat mass and lean mass.[106,107] The precision of soft-tissue analysis of two DXA devices – the GE Lunar iDXA and the GE Lunar Prodigy – was compared and reported to be 0.8% (iDXA) vs 2.5% (Prodigy) for total body fat.[107] Thus the iDXA provided excellent precision for measurements of body composition in a heterogeneous sample of men and women.

For rheumatologists, DXA is known to be a valid method to estimate body composition in RA patients, and furthermore, changes in body composition may contribute to the increased morbidity as well as the mortality associated with RA.[106,108,109]

The condition of "rheumatoid cachexia" (RC) has been described in RA and is thought to be a result of cytokine-driven hypermetabolism and protein degradation, causing a reduction of fat-free mass with a concurrent increase in body-fat mass.[110,111] These body-composition changes of RC have been described in up two-thirds of RA patients and put them at risk for cardiovascular and metabolic morbidity as well as muscle weakness, infections, and disability.[111–115] Of further concern, however, is the finding that RA patients have evidence of RC, even when assessed during periods when the disease is well controlled. Anti-TNF treatments and increased protein intake have not been shown to reverse RC, although weight training can help.[115,116]

Therefore, analyzing body composition with DXA can be of great importance when assessing RA patients in clinical practice.

Summary

The clinical practice of rheumatology demonstrates a significant need for the use of DXA in order to discover patients with osteoporosis and high fracture risk, as well as to monitor changes with time due to the treatment or the underlying condition.

The widespread use of GC treatment for various rheumatologic conditions has created a secondary problem with GC-induced osteoporosis and thus the need for rheumatologists to incorporate DXA bone density measurement into their practice. GCs used to treat inflammatory diseases as well as the underlying rheumatological condition lead to bone loss and an increased fracture risk, which is further compounded by musculoskeletal functional decline and increased fall and fracture risk.

Various guidelines and the WHO FRAX tool have established DXA and knowledge of rheumatological conditions as essential for recognizing fracture risk and associated complications. While only RA and GC use are included in FRAX clinical risk factors, other rheumatologic conditions increase risk of bone loss and fracture risk. The binary nature of the FRAX risk factors may lead to an underestimation of fracture risk in the case of GC use.

Strategies to assure patient access to DXA services are an imperative component of rheumatology care. Optimal use of DXA requires a thorough understanding of the application of the technology, including bone-density measurement, vertebral fracture assessment, and body-composition analysis, along with attention to quality in acquisition, analysis, and interpretation.

Disclosure

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