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REVIEW

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.

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References

1. Pereira RM, Carvalho JF, Canalis E. Glucocorticoid-induced osteoporosis in rheumatic diseases. *Clinics (Sao Paulo)*. 2010;65(11):1197–1205.
2. Ding C, Parameswaran V, Udayan R, Burgess J, Jones G. Circulating levels of inflammatory markers predict change in bone mineral density and resorption in older adults: a longitudinal study. *J Clin Endocrinol Metab*. 2008;93(5):1952–1958.
3. Broy SB, Tanner SB. Official positions for FRAX clinical regarding rheumatoid arthritis from Joint Official Positions Development Conference of the International Society for Clinical Densitometry and International Osteoporosis Foundation on FRAX. *J Clin Densitom*. 2011;14(3):184–189.
4. Johnston CC, Melton LJ, Lindsay R, Eddy DM. Clinical indications for bone measurements. A report from the scientific advisory board of the National Osteoporosis Foundation. *J Bone Miner Res*. 1989;4 Suppl 2:1–28.
5. United States General Accounting Office (GAO). Medicare Coverage of and Payment for Bone Mass Measurements. Washington: GAO; 1998.

6. Watts NB. Understanding the Bone Mass Measurement Act. *J Clin Densitom*. 1999;2(3):211–217.
7. Kanis JA. Assessment of fracture risk and its application to screening for postmenopausal osteoporosis: synopsis of a WHO report. WHO Study Group. *Osteoporos Int*. 1994;4(6):368–381.
8. Kanis JA, Johnell O, Oden A, Johansson H, McCloskey E. FRAX and the assessment of fracture probability in men and women from the UK. *Osteoporos Int*. 2008;19(4):385–397.
9. Hans DB, Kanis JA, Baim S, et al. Joint official positions of the International Society for Clinical Densitometry and International Osteoporosis Foundation on FRAX. Executive Summary of the 2010 Position Development Conference on Interpretation and Use of FRAX in Clinical Practice. *J Clin Densitom*. 2011;14(3):171–180.
10. Dawson-Hughes B, Tosteson AN, Melton LJ 3rd, et al. Implications of absolute fracture risk assessment for osteoporosis practice guidelines in the USA. *Osteoporos Int*. 2008;19(4):449–458.
11. Lewiecki EM, Watts NB. New guidelines for the prevention and treatment of osteoporosis. *South Med J*. 2009;102(2):175–179.
12. Krieg MA, Barkmann R, Gonnelli S, et al. Quantitative ultrasound in the management of osteoporosis: the 2007 ISCD official positions. *J Clin Densitom*. 2008;11(1):163–187.
13. Chan MY, Nguyen ND, Center JR, Eisman JA, Nguyen TV. Quantitative ultrasound and fracture risk prediction in non-osteoporotic men and women as defined by WHO criteria. *Osteoporos Int*. Epub August 10, 2012.
14. Nguyen ND, Frost SA, Center JR, Eisman JA, Nguyen TV. Development of prognostic nomograms for individualizing 5-year and 10-year fracture risks. *Osteoporos Int*. 2008;19(10):1431–1444.
15. Wu Q, Magnus JH, Rice JC, Lefante JJ. Does using lower limit of normal values enhance the ability of a single bone mineral density measure to predict fractures? *Osteoporos Int*. 2010;21(11):1881–1888.
16. Wu Q, Lefante JJ, Rice JC, Magnus JH. Age, race, weight, and gender impact normative values of bone mineral density. *Gend Med*. 2011;8(3):189–201.
17. Lewiecki EM. Bone densitometry and vertebral fracture assessment. *Curr Osteoporos Rep*. 2010;8(3):123–130.
18. Hayes BL, Curtis JR, Laster A, et al. Osteoporosis care in the United States after declines in reimbursements for DXA. *J Clin Densitom*. 2010;13(4):352–360.
19. Tanner SB. Dual-energy X-ray absorptiometry in clinical practice: new guidelines and concerns. *Curr Opin Rheumatol*. 2011;23(4):385–388.
20. King AB, Fiorentino DM. Medicare payment cuts for osteoporosis testing reduced use despite tests' benefit in reducing fractures. *Health Aff (Millwood)*. 2011;30(12):2362–2370.
21. O'Malley CD, Johnston SS, Lenhart G, Cherkowski G, Palmer L, Morgan SL. Trends in dual-energy X-ray absorptiometry in the United States, 2000–2009. *J Clin Densitom*. 2011;14(2):100–107.
22. [No authors listed]. Recommendations for the prevention and treatment of glucocorticoid-induced osteoporosis. American College of Rheumatology Task Force on Osteoporosis Guidelines. *Arthritis Rheum*. 1996;39(11):1791–1801.
23. Lewiecki EM. Review of guidelines for bone mineral density testing and treatment of osteoporosis. *Curr Osteoporos Rep*. 2005;3(3):75–83.
24. [No authors listed]. Recommendations for the prevention and treatment of glucocorticoid-induced osteoporosis: 2001 update. American College of Rheumatology Ad Hoc Committee on Glucocorticoid-Induced Osteoporosis. *Arthritis Rheum*. 2001;44(7):1496–1503.
25. Grossman JM, Gordon R, Ranganath VK, et al. American College of Rheumatology 2010 recommendations for the prevention and treatment of glucocorticoid-induced osteoporosis. *Arthritis Care Res (Hoboken)*. 2010;62(11):1515–1526.
26. Kirigaya D, Nakayama T, Ishizaki T, Ikeda S, Satoh T. Management and treatment of osteoporosis in patients receiving long-term glucocorticoid treatment: current status of adherence to clinical guidelines and related factors. *Intern Med*. 2011;50(22):2793–2800.
27. van der Goes MC, Jacobs JW, Boers M, et al. Monitoring adverse events of low-dose glucocorticoid therapy: EULAR recommendations for clinical trials and daily practice. *Ann Rheum Dis*. 2010;69(11):1913–1919.
28. Weinstein RS. Clinical practice. Glucocorticoid-induced bone disease. *N Engl J Med*. 2011;365(1):62–70.
29. van Staa TP, Leufkens HG, Cooper C. The epidemiology of corticosteroid-induced osteoporosis: a meta-analysis. *Osteoporos Int*. 2002;13(10):777–787.
30. Lekamwasam S, Adachi JD, Agnusdei D, et al. A framework for the development of guidelines for the management of glucocorticoid-induced osteoporosis. *Osteoporos Int*. Epub March 21, 2012.
31. Compston JE. Emerging consensus on prevention and treatment of glucocorticoid-induced osteoporosis. *Curr Rheumatol Rep*. 2007;9(1):78–84.
32. Van Staa TP, Laan RF, Barton IP, Cohen S, Reid DM, Cooper C. Bone density threshold and other predictors of vertebral fracture in patients receiving oral glucocorticoid therapy. *Arthritis Rheum*. 2003;48(11):3224–3229.
33. Luengo M, Picado C, Del Rio L, Guanabens N, Montserrat JM, Setoain J. Treatment of steroid-induced osteopenia with calcitonin in corticosteroid-dependent asthma. A one-year follow-up study. *Am Rev Respir Dis*. 1990;142(1):104–107.
34. Kanis JA, Johansson H, Oden A, et al. A meta-analysis of prior corticosteroid use and fracture risk. *J Bone Miner Res*. 2004;19(6):893–899.
35. Canalis E, Mazziotti G, Giustina A, Bilezikian JP. Glucocorticoid-induced osteoporosis: pathophysiology and therapy. *Osteoporos Int*. 2007;18(10):1319–1328.
36. Leib ES, Saag KG, Adachi JD, et al. Official positions for FRAX clinical regarding glucocorticoids: the impact of the use of glucocorticoids on the estimate by FRAX of the 10 year risk of fracture from Joint Official Positions Development Conference of the International Society for Clinical Densitometry and International Osteoporosis Foundation on FRAX. *J Clin Densitom*. 2011;14(3):212–219.
37. Compston J. Clinical question: What is the best approach to managing glucocorticoid-induced osteoporosis? *Clin Endocrinol (Oxf)*. 2011;74(5):547–550.
38. van Staa TP, Geusens P, Bijlsma JW, Leufkens HG, Cooper C. Clinical assessment of the long-term risk of fracture in patients with rheumatoid arthritis. *Arthritis Rheum*. 2006;54(10):3104–3112.
39. Kvien TK, Haugeberg G, Uhlig T, et al. Data driven attempt to create a clinical algorithm for identification of women with rheumatoid arthritis at high risk of osteoporosis. *Ann Rheum Dis*. 2000;59(10):805–811.
40. Lane NE, Pressman AR, Star VL, Cummings SR, Nevitt MC. Rheumatoid arthritis and bone mineral density in elderly women. The Study of Osteoporotic Fractures Research Group. *J Bone Miner Res*. 1995;10(2):257–263.
41. Laan RF, Buijs WC, Verbeek AL, et al. Bone mineral density in patients with recent onset rheumatoid arthritis: influence of disease activity and functional capacity. *Ann Rheum Dis*. 1993;52(1):21–26.
42. Haugeberg G, Uhlig T, Falch JA, Halse JI, Kvien TK. Bone mineral density and frequency of osteoporosis in female patients with rheumatoid arthritis: results from 394 patients in the Oslo County Rheumatoid Arthritis register. *Arthritis Rheum*. 2000;43(3):522–530.
43. Sambrook PN, Eisman JA, Champion GD, Yeates MG, Pocock NA, Eberl S. Determinants of axial bone loss in rheumatoid arthritis. *Arthritis Rheum*. 1987;30(7):721–728.
44. Kim SY, Schneeweiss S, Liu J, et al. Risk of osteoporotic fracture in a large population-based cohort of patients with rheumatoid arthritis. *Arthritis Res Ther*. 2010;12(4):R154.
45. Cooper C, Coupland C, Mitchell M. Rheumatoid arthritis, corticosteroid therapy and hip fracture. *Ann Rheum Dis*. 1995;54(1):49–52.
46. Huusko TM, Korpela M, Karppi P, Avikainen V, Kautiainen H, Sulkava R. Threefold increased risk of hip fractures with rheumatoid arthritis in Central Finland. *Ann Rheum Dis*. 2001;60(5):521–522.
47. Hooyman JR, Melton LJ 3rd, Nelson AM, O'Fallon WM, Riggs BL. Fractures after rheumatoid arthritis. a population-based study. *Arthritis Rheum*. 1984;27(12):1353–1361.

48. Spector TD, Hall GM, McCloskey EV, Kanis JA. Risk of vertebral fracture in women with rheumatoid arthritis. *BMJ*. 1993;306(6877):558.
49. Baskan BM, Sivas F, Alemdaroglu E, Duran S, Ozoran K. Association of bone mineral density and vertebral deformity in patients with rheumatoid arthritis. *Rheumatol Int*. 2007;27(6):579–584.
50. Orstavik RE, Haugeberg G, Mowinckel P, et al. Vertebral deformities in rheumatoid arthritis: a comparison with population-based controls. *Arch Intern Med*. 2004;164(4):420–425.
51. Haugeberg G, Uhlig T, Falch JA, Halse JI, Kvien TK. Reduced bone mineral density in male rheumatoid arthritis patients: frequencies and associations with demographic and disease variables in ninety-four patients in the Oslo County Rheumatoid Arthritis Register. *Arthritis Rheum*. 2000;43(12):2776–2784.
52. Cauley JA, Danielson ME, Boudreau RM, et al. Inflammatory markers and incident fracture risk in older men and women: the Health Aging and Body Composition Study. *J Bone Miner Res*. 2007;22(7):1088–1095.
53. Kaz Kaz H, Johnson D, Kerry S, Chinappen U, Tweed K, Patel S. Fall-related risk factors and osteoporosis in women with rheumatoid arthritis. *Rheumatology (Oxford)*. 2004;43(10):1267–1271.
54. Smulders E, Schreven C, Weerdesteyn V, van den Hoogen FH, Laan R, Van Lankveld W. Fall incidence and fall risk factors in people with rheumatoid arthritis. *Ann Rheum Dis*. 2009;68(11):1795–1796.
55. Arai K, Hanyu T, Sugitani H, et al. Risk factors for vertebral fracture in menopausal or postmenopausal Japanese women with rheumatoid arthritis: a cross-sectional and longitudinal study. *J Bone Miner Metab*. 2006;24(2):118–124.
56. Furuya T, Kotake S, Inoue E, et al. Risk factors associated with incident clinical vertebral and nonvertebral fractures in Japanese women with rheumatoid arthritis: a prospective 54-month observational study. *J Rheumatol*. 2007;34(2):303–310.
57. Vestergaard P, Rejnmark L, Mosekilde L. Methotrexate, azathioprine, cyclosporine, and risk of fracture. *Calcif Tissue Int*. 2006;79(2):69–75.
58. Urano W, Furuya T, Inoue E, et al. Associations between methotrexate treatment and methylenetetrahydrofolate reductase gene polymorphisms with incident fractures in Japanese female rheumatoid arthritis patients. *J Bone Miner Metab*. 2009;27(5):574–583.
59. Coulson KA, Reed G, Gilliam BE, Kremer JM, Pepmueller PH. Factors influencing fracture risk, T score, and management of osteoporosis in patients with rheumatoid arthritis in the Consortium of Rheumatology Researchers of North America (CORRONA) registry. *J Clin Rheumatol*. 2009;15(4):155–160.
60. Ramsey-Goldman R, Dunn JE, Huang CF, et al. Frequency of fractures in women with systemic lupus erythematosus: comparison with United States population data. *Arthritis Rheum*. 1999;42(5):882–890.
61. Bultink IE. Osteoporosis and fractures in systemic lupus erythematosus. *Arthritis Care Res (Hoboken)*. 2012;64(1):2–8.
62. Bultink IE, Lems WF, Kostense PJ, Dijkmans BA, Voskuyl AE. Prevalence of and risk factors for low bone mineral density and vertebral fractures in patients with systemic lupus erythematosus. *Arthritis Rheum*. 2005;52(7):2044–2050.
63. Lakshminarayanan S, Walsh S, Mohanraj M, Rothfield N. Factors associated with low bone mineral density in female patients with systemic lupus erythematosus. *J Rheumatol*. 2001;28(1):102–108.
64. Almehed K, Forsblad d'Elia H, Kvist G, Ohlsson C, Carlsten H. Prevalence and risk factors of osteoporosis in female SLE patients – extended report. *Rheumatology (Oxford)*. 2007;46(7):1185–1190.
65. Redlich K, Ziegler S, Kiener HP, et al. Bone mineral density and biochemical parameters of bone metabolism in female patients with systemic lupus erythematosus. *Ann Rheum Dis*. Apr 2000;59(4):308–310.
66. Im CH, Kang EH, Ki JY, et al. Receptor activator of nuclear factor kappa B ligand-mediated osteoclastogenesis is elevated in ankylosing spondylitis. *Clin Exp Rheumatol*. 2009;27(4):620–625.
67. Roux C. Osteoporosis in inflammatory joint diseases. *Osteoporos Int*. 2011;22(2):421–433.
68. Briot K, Gossec L, Kolta S, Dougados M, Roux C. Prospective assessment of body weight, body composition, and bone density changes in patients with spondyloarthropathy receiving anti-tumor necrosis factor-alpha treatment. *J Rheumatol*. 2008;35(5):855–861.
69. Vasdev V, Bhakuni D, Garg MK, Narayanan K, Jain R, Chadha D. Bone mineral density in young males with ankylosing spondylitis. *Int J Rheum Dis*. 2011;14(1):68–73.
70. El Maghraoui A, Borderie D, Cherruau B, Edouard R, Dougados M, Roux C. Osteoporosis, body composition, and bone turnover in ankylosing spondylitis. *J Rheumatol*. 1999;26(10):2205–2209.
71. Capaci K, Hepguler S, Argin M, Tas I. Bone mineral density in mild and advanced ankylosing spondylitis. *Yonsei Med J*. 2003;44(3):379–384.
72. Ghozlani I, Ghazi M, Nouijai A, et al. Prevalence and risk factors of osteoporosis and vertebral fractures in patients with ankylosing spondylitis. *Bone*. 2009;44(5):772–776.
73. Bessant R, Keat A. How should clinicians manage osteoporosis in ankylosing spondylitis? *J Rheumatol*. 2002;29(7):1511–1519.
74. Cooper C, Carbone L, Michet CJ, Atkinson EJ, O'Fallon WM, Melton LJ 3rd. Fracture risk in patients with ankylosing spondylitis: a population based study. *J Rheumatol*. 1994;21(10):1877–1882.
75. Baim S, Leonard MB, Bianchi ML, et al. Official positions of the International Society for Clinical Densitometry and executive summary of the 2007 ISCD Pediatric Position Development Conference. *J Clin Densitom*. 2008;11(1):6–21.
76. Rauch F, Plotkin H, DiMeglio L, et al. Fracture prediction and the definition of osteoporosis in children and adolescents: the ISCD 2007 Pediatric Official Positions. *J Clin Densitom*. 2008;11(1):22–28.
77. Roth J, Bechtold S, Borte G, Dressler F, Girschick HJ, Borte M. Osteoporosis in juvenile idiopathic arthritis – a practical approach to diagnosis and therapy. *Eur J Pediatr*. 2007;166(8):775–784.
78. Zak M, Hassager C, Lovell DJ, Nielsen S, Henderson CJ, Pedersen FK. Assessment of bone mineral density in adults with a history of juvenile chronic arthritis: a cross-sectional long-term followup study. *Arthritis Rheum*. Apr 1999;42(4):790–798.
79. Elsasser U, Wilkins B, Hesp R, Thurnham DI, Reeve J, Ansell BM. Bone rarefaction and crush fractures in juvenile chronic arthritis. *Arch Dis Child*. 1982;57(5):377–380.
80. Pepmueller PH, Cassidy JT, Allen SH, Hillman LS. Bone mineralization and bone mineral metabolism in children with juvenile rheumatoid arthritis. *Arthritis Rheum*. 1996;39(5):746–757.
81. Lurati A, Cimaz R, Gattinara M, et al. Skeletal mineralization in a prepubertal female population affected by juvenile idiopathic arthritis. *Reumatismo*. 2008;60(3):224–229. Italian.
82. Varonos S, Ansell BM, Reeve J. Vertebral collapse in juvenile chronic arthritis: its relationship with glucocorticoid therapy. *Calcif Tissue Int*. 1987;41(2):75–78.
83. Nikpour M, Stevens WM, Herrick AL, Proudman SM. Epidemiology of systemic sclerosis. *Best Pract Res Clin Rheumatol*. 2010;24(6):857–869.
84. Carbone L, Tylavsky F, Wan J, McKown K, Cheng S. Bone mineral density in scleroderma. *Rheumatology (Oxford)*. 1999;38(4):371–372.
85. Di Munno O, Mazzantini M, Massei P, et al. Reduced bone mass and normal calcium metabolism in systemic sclerosis with and without calcinosis. *Clin Rheumatol*. 1995;14(4):407–412.
86. La Montagna G, Vatti M, Valentini G, Tirri G. Osteopenia in systemic sclerosis. Evidence of a participating role of earlier menopause. *Clin Rheumatol*. 1991;10(1):18–22.
87. Frediani B, Baldi F, Falsetti P, et al. Bone mineral density in patients with systemic sclerosis. *Ann Rheum Dis*. 2004;63(3):326–327.
88. Souza RB, Borges CT, Takayama L, Aldrighi JM, Pereira RM. Systemic sclerosis and bone loss: the role of the disease and body composition. *Scand J Rheumatol*. 2006;35(5):384–387.
89. Sampaio-Barros PD, Costa-Paiva L, Filardi S, Sachetto Z, Samara AM, Marques-Neto JF. Prognostic factors of low bone mineral density in systemic sclerosis. *Clin Exp Rheumatol*. 2005;23(2):180–184.

90. Frediani B, Baldi F, Falsetti P, et al. Clinical determinants of bone mass and bone ultrasonometry in patients with systemic sclerosis. *Clin Exp Rheumatol*. 2004;22(3):313–318.
91. Yuen SY, Rochwerg B, Ouimet J, Pope JE. Patients with scleroderma may have increased risk of osteoporosis. A comparison to rheumatoid arthritis and noninflammatory musculoskeletal conditions. *J Rheumatol*. 2008;35(6):1073–1078.
92. Neumann K, Wallace DJ, Metzger AL. Osteoporosis – less than expected in patients with scleroderma? *J Rheumatol*. 2000;27(7):1822–1823.
93. Rios Fernandez R, Fernandez Roldan C, Callejas Rubio JL, Ortego Centeno N. Vitamin D deficiency in a cohort of patients with systemic scleroderma from the south of Spain. *J Rheumatol*. 2010;37(6):1355;author reply 1356.
94. Loucks J, Pope JE. Osteoporosis in scleroderma. *Semin Arthritis Rheum*. 2005;34(4):678–682.
95. Cooper C, Atkinson EJ, O'Fallon WM, Melton LJ 3rd. Incidence of clinically diagnosed vertebral fractures: a population-based study in Rochester, Minnesota, 1985–1989. *J Bone Miner Res*. 1992;7(2):221–227.
96. Schlaich C, Minne HW, Bruckner T, et al. Reduced pulmonary function in patients with spinal osteoporotic fractures. *Osteoporos Int*. 1998;8(3):261–267.
97. Nevitt MC, Ettinger B, Black DM, et al. The association of radiographically detected vertebral fractures with back pain and function: a prospective study. *Ann Intern Med*. 1998;128(10):793–800.
98. Kado DM, Browner WS, Palermo L, Nevitt MC, Genant HK, Cummings SR. Vertebral fractures and mortality in older women: a prospective study. Study of Osteoporotic Fractures Research Group. *Arch Intern Med*. 1999;159(11):1215–1220.
99. Ensrud KE, Thompson DE, Cauley JA, et al. Prevalent vertebral deformities predict mortality and hospitalization in older women with low bone mass. Fracture Intervention Trial Research Group. *J Am Geriatr Soc*. 2000;48(3):241–249.
100. Jacobs-Kosmin D, Sandorfi N, Murray H, Abruzzo JL. Vertebral deformities identified by vertebral fracture assessment: associations with clinical characteristics and bone mineral density. *J Clin Densitom*. 2005;8(3):267–272.
101. Rea JA, Chen MB, Li J, et al. Morphometric X-ray absorptiometry and morphometric radiography of the spine: a comparison of prevalent vertebral deformity identification. *J Bone Miner Res*. 2000;15(3):564–574.
102. Rea JA, Li J, Blake GM, Steiger P, Genant HK, Fogelman I. Visual assessment of vertebral deformity by X-ray absorptiometry: a highly predictive method to exclude vertebral deformity. *Osteoporos Int*. 2000;11(8):660–668.
103. Ferrar L, Jiang G, Eastell R, Peel NF. Visual identification of vertebral fractures in osteoporosis using morphometric X-ray absorptiometry. *J Bone Miner Res*. 2003;18(5):933–938.
104. Ghazi M, Kolta S, Briot K, Fechtenbaum J, Paternotte S, Roux C. Prevalence of vertebral fractures in patients with rheumatoid arthritis: revisiting the role of glucocorticoids. *Osteoporos Int*. 2012;23(2):581–587.
105. Roux C, Baron G, Audran M, et al. Influence of vertebral fracture assessment by dual-energy X-ray absorptiometry on decision-making in osteoporosis: a structured vignette survey. *Rheumatology (Oxford)*. 2011;50(12):2264–2269.
106. Elkan AC, Engvall IL, Cederholm T, Hafstrom I. Rheumatoid cachexia, central obesity and malnutrition in patients with low-active rheumatoid arthritis: feasibility of anthropometry, Mini Nutritional Assessment and body composition techniques. *Eur J Nutr*. 2009;48(5):315–322.
107. Hind K, Oldroyd B, Truscott JG. In vivo precision of the GE Lunar iDXA densitometer for the measurement of total body composition and fat distribution in adults. *Eur J Clin Nutr*. 2011;65(1):140–142.
108. Podenphant J, Gotfredsen A, Engelhart M, Andersen V, Heitmann BL, Kondrup J. Comparison of body composition by dual energy X-ray absorptiometry to other estimates of body composition during weight loss in obese patients with rheumatoid arthritis. *Scand J Clin Lab Invest*. 1996;56(7):615–625.
109. Sun G, French CR, Martin GR, et al. Comparison of multifrequency bioelectrical impedance analysis with dual-energy X-ray absorptiometry for assessment of percentage body fat in a large, healthy population. *Am J Clin Nutr*. 2005;81(1):74–78.
110. Roubenoff R, Roubenoff RA, Ward LM, Holland SM, Hellmann DB. Rheumatoid cachexia: depletion of lean body mass in rheumatoid arthritis. Possible association with tumor necrosis factor. *J Rheumatol*. 1992;19(10):1505–1510.
111. Walsmith J, Roubenoff R. Cachexia in rheumatoid arthritis. *Int J Cardiol*. 2002;85(1):89–99.
112. Maradit-Kremers H, Nicola PJ, Crowson CS, Ballman KV, Gabriel SE. Cardiovascular death in rheumatoid arthritis: a population-based study. *Arthritis Rheum*. 2005;52(3):722–732.
113. Rall LC, Roubenoff R. Rheumatoid cachexia: metabolic abnormalities, mechanisms and interventions. *Rheumatology (Oxford)*. 2004;43(10):1219–1223.
114. Rajbhandary R, Khezri A, Panush RS. Rheumatoid cachexia: what is it and why is it important? *J Rheumatol*. 2011;38(3):406–408.
115. Lemmey AB, Jones J, Maddison PJ. Rheumatoid cachexia: what is it and why is it important? *J Rheumatol*. 2011;38(9):2074;author reply 2075.
116. Cooney JK, Law RJ, Matschke V, et al. Benefits of exercise in rheumatoid arthritis. *J Aging Res*. 2011;2011:681640.