Clinical utilities of quantitative ultrasound in osteoporosis associated with inflammatory rheumatic diseases

Win Min Oo1, Vasikaran Naganathan2, Myat Thae Bo3, David J. Hunter1

1Rheumatology Department, Royal North Shore Hospital, and Institute of Bone and Joint Research, Kolling Institute, University of Sydney, Sydney, Australia; 2Centre for Education and Research on Ageing and the Ageing and Alzheimer’s Institute, Sydney Medical School, The University of Sydney and Concord Hospital, Sydney, Australia; 3University of Medicine-Mandalay, Mandalay, Myanmar

Correspondence to: Win Min Oo. Rheumatology Department, Royal North Shore Hospital, and Institute of Bone and Joint Research, Kolling Institute, University of Sydney, Sydney, Australia. Email: wioo3335@uni.sydney.edu.au; winminoo@ummdy.com.

Abstract: Secondary osteoporosis is an important co-morbidity related to inflammatory rheumatic diseases that is attributed to several factors including inflammatory cytokines, inactivity and glucocorticoid treatment. Quantitative ultrasound (QUS) has been utilized in osteoporosis research due to its detectability of bone density as well as bone quality. The current narrative review is to address the potential utilities of QUS in secondary osteoporosis of inflammatory rheumatic diseases, focusing on the clinical aspects of QUS in these diseases, based on the conformity of QUS with dual emission X-ray absorptiometry (DXA), the relationship with disease characteristics, and its capability of fracture prediction. Although limited data demonstrate that QUS had moderate to strong correlation with DXA, and might be useful as a potential imaging tool to screen for osteoporosis, further research is still required for QUS to be utilized effectively for the best outcome in these patients with rheumatic diseases.

Keywords: Quantitative ultrasound (QUS); osteoporosis; inflammatory rheumatic disease; review; fracture

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Introduction

Osteoporosis is characterized by reduced bone mass and microarchitectural deterioration of bone tissue, with consequent bone fragility and susceptibility to fractures (1). There are different defining criteria of osteoporosis on the basis of adult or pediatric populations. For adults, the WHO’s operational definition for osteoporosis specifies bone density of 2.5 standard deviations (SD) (T-scores) or more below the mean for young healthy adult women in dual emission X-ray absorptiometry (DXA), and osteopenia is defined as a T-score between −1 and −2.5 (2). In the pediatric population, the International Society of Clinical Densitometry determined low bone mineral density as a Z-score (not T-score) below −2.0 in children (3), and so it is not appropriate for growing children (4).

Osteoporosis is one of the most ubiquitous skeletal diseases, with 10 million individuals currently diagnosed in the United States (5) and 2 million having osteoporotic fractures for each year (6). Osteoporotic fractures are closely associated with increased mortality. About 20–30% of patients with osteoporotic fracture die due to long-term immobilization and postoperative complications within 6 months (7). Therefore, the ability to diagnose osteoporosis before fractures occur, and timely treatment of osteoporosis are important.

From a pathological point of view, in osteoporosis, radiological imaging plays a role in the identification of early bone weakening and evaluation of patterns of bone alterations (8). From a clinical point of view, radiological imaging is used for fracture risk prediction, screening for the osteoporosis, deciding on the choice of the treatment,
and monitoring disease progression and therapeutic response (9).

### Prevalence of osteoporosis in inflammatory rheumatic diseases

The prevalence of osteoporosis varies broadly, depending on the particular types of rheumatic diseases as shown in Table 1. Even when the same WHO defining criteria for osteoporosis in terms of DXA was applied to a specific disease, inconsistent prevalence estimates are detected across the studies as a result of several factors such as characteristics of study population, age and sex of participants, disease activity, disease duration, treatment received, concomitant glucocorticoid therapy and site of BMD measurement (10,11,31). In the cross-sectional study, the low bone mineral density (BMD) in lumbar spine and hip was reported in 45% of adult who had a history of juvenile idiopathic arthritis (JIA) in childhood (32). So, the full remission of the disease in young adults cannot completely normalize BMD at all skeletal sites (33), posing them at risk of developing premature osteoporosis and associated fractures later in life. Osteoporosis, therefore, imposes a large burden on patients with inflammatory rheumatic diseases.

Secondary osteoporosis is an important co-morbidity in rheumatic disorders due to several mechanisms including the effects of inflammation on bone modeling, which increase osteoclast activation and subsequent bone resorption mediated by proinflammatory cytokines (34), physical inactivity attributed to painful joints and muscle weakness, increasing the osteoporosis risk, and the adverse skeletal effects related to the therapies administered to treat these diseases, e.g. glucocorticoids (GC) (Figure 1) (35,36). Substantial evidence shows that cross-talk between inflammatory cells and bone cells leads to production of a wide spectrum of cytokines such as interleukin-6 (IL-6), tumor necrosis factor (TNF), C-reactive protein (CRP), receptor activator of nuclear factor kappa-β ligand (RANKL) at sites of inflammation, that stimulate local and generalized bone resorption, and that inhibit in RA, or stimulate in AS, bone formation (37,38).

### Bone density

Bone composition includes mineral, mainly calcium hydroxyapatite, embedded in type I collagen and specialized proteins forming the bone matrix. Calcium absorbs much more radiation than protein or soft tissue. The amount of X-ray energy that is absorbed by calcium in a section reflects the bone mineral content (BMC), which is divided by the area or volume of the bone to get estimated bone densitometry (BMD).

In laboratory studies, there is a high correlation (r=0.62) between BMD and bone breaking strength (39). Other determinants of bone strength include size, macroscopic structure (long bones with greater cross-sectional areas are more resistant to bending forces), microscopic structure (loss of normal trabecular architecture), and the composition of bone proteins (abnormal collagen) (40).

Bone evaluation to quantify BMD can be performed by various methods, including dual-emission X-ray absorptiometry (DXA), quantitative ultrasound (QUS) and quantitative computed tomography (QCT).

### Quantitative methods

#### DXA

Bone densitometry utilizing DXA is the most widely used
quantitative technique in clinical practice, and remains the gold-standard test for the osteoporosis diagnosis and quantification. Of all modalities, it has the most data on predicting fractures in post-menopausal women in longitudinal population-based studies (41).

Lumbar spine is the primary site for BMD measurement, either providing total spine (from L1 to L4) or individual vertebral T-scores (9). Vertebral bodies largely comprise trabecular bone, possess a high ratio of remodeling surface to bone volume, and so are more sensitive to treatment or disease changes than cortical bone in other sites. The other most common sites of measurements are the hip region including femoral neck, trochanter, Ward's area, intertrochanteric region, and total hip respectively, with the BMD of proximal femur being the best predictor of hip fracture (25) while lumbar spine bone mineral density does best in monitoring treatment effects (26).

However, spine BMD can be overestimated in degenerative arthritis, aortic calcification, etc. as standard anteroposterior spine BMD includes mineral in the posterior elements and facet joints as well as the abdominal aorta. Caution should, therefore, be exercised in interpreting spine BMD after about age 65 years (42).

As it is assessed in 2 dimensions, the section size of the bone has an impact on it: if a large and a small bone have the same mineral density, the larger will appear to have a higher BMD (Figure 2). Care should therefore be taken in interpreting longitudinal measurements of BMD in pediatric population such as in JIA due to potential size effects (4).

Another serious limitation of DXA is the inability of DXA to evaluate bone quality and microarchitecture of the trabeculae, which correspond to up to 50% of the mechanical strength of bone, representing a relationship of 0.43 between bone density and bone strength (44). This association explains why the fracture risk (the ultimate complication of osteoporosis) may be greater than the DXA would suggest, highlighting the importance of the fragile bone microarchitecture. In addition, this method incurs some major disadvantages, such as little information about cortical bone properties, the necessity of radiation exposure, limited accessibility, the need of some trained personnel, overestimations of bone density by marginal osteophyte (45) and vascular calcifications projecting on lumbar spine (46), and high cost.

In addition, DXA has several other limitations in measuring osteoporosis related with inflammatory arthritis as a result of the negative impact of inflammatory cytokines on bone health (36,47) and the required use of glucocorticoid in these diseases (48,49). In rheumatoid arthritis patients, treated with GC, the risk of vertebral fracture has been reported as having increased 6-fold compared with controls, whereas the reduction of lumbar spine BMD was only 0.79 SD (50). A recent meta-analysis on glucocorticoid-induced osteoporosis revealed that fractures occur at a much higher rate than expected on the basis of BMD, and that BMD changes during GC therapy may predict, only to a moderate extent, the increase in fracture risk (49).
QCT

QCT produces volumetric 3D measurements by using low-dose scan protocols on a standard CT scanner for the spine (axial QCT) or by working on dedicated extremity scanner for peripheral quantitative computed tomography (pQCT). Axial QCT measures trabecular bone in spinal vertebrae and usually scans between T11 and L4 in 2D single slice QCT of the spine or includes only two vertebrae, often L1 and L2, in the case of spiral multi-detector CT to reduce radiation dose (51) (Figure 3). Fractured vertebrae should not be analyzed as the inclusion of the endplate will overestimate the BMD. An oval region of interest with as much of the vertebral trabecular bone as possible, without the inclusion of the cortical rim or basi-vertebral vein, is selected for providing the trabecular BMD in mg/cm$^3$ of individual vertebrae scanned. The result is compared with a phantom as bone mineral reference standard to calibrate each scan, and usually expressed in absolute values or as Z-scores and T-scores.

QCT has some limitations such as the effect of marrow changes on trabecular measurements (myelofibrosis, hematopoietic disorders, etc), expensiveness (51), high radiation dose (90 to 3,000 µSv) compared with DXA (1–6 µSv) (53,54), lack of standardization of examinations among the CT devices produced by different manufacturers (55) and the partial volume effect (underestimation of cortical BMD when the thickness of the cortical bone shell is less than 2 mm), which happens when a voxel in the image represents more than one tissue (56).

QUS

The use of QUS to investigate osteoporosis in cancellous heel bone was first introduced in 1984 (57), and involves placing ultrasound transducers on either side of the calcaneus; one acts as a wave transmitter and the other acts as the receiver (58). The transmission of ultrasound of frequency range between 200 and 1.5 MHz through bone tissue reflects its density and its structure (59). The majority of QUS research in the literature has focused on the calcaneal site as it has a high metabolic activity and demineralization pattern similar to the spine (60), although some other sites such as patella, tibia, phalanges and radius have also been studied.

The two main parameters measured in QUS are: broadband ultrasound attenuation (BUA) in decibel per megahertz and speed of sound (SOS) in meters per second. From these measures, a number of other measures can be derived including stiffness index, QUS index, amplitude-dependent speed of sound (AD-SoS), and bone transmission time (BTT) (61) (Figure 4).

BUA represents a measure of the ultrasound variation of attenuation with the incident frequency of sound wave, primarily by absorption in cortical bone and scattering in the cancellous bone (63), and is expressed on a logarithmic scale over the range 0.1–1 MHz. SOS measures the distance the ultrasound signal travels per unit of time, independent of ultrasound wave attenuation (64). BUA and SOS parameters are usually measured by QUS devices used for heel, radius, tibia and patella (Figure 5) (62).
QUS index and stiffness are composite parameters derived from BUA and SOS, or velocity of sound (VOS), and described as a percentage of the result from young adults or the percentage of weight-matched references according to the manufacturer (65). QUS measures can be recorded in absolute values, or in T-score and Z-score compared to normative reference data (9). AD-SoS measures the interval from the starting time of the transmitted signal until the predetermined minimum amplitude of 2 mV is reached for the first time by the ultrasound signal received. BTT reflects the bone properties independent of the confounding effect of soft tissue and expressed in microsecond. AD-SoS and BTT are primarily quantified by the phalangeal QUS device (62).

In vitro studies, SOS is closely associated with bone mineralization with a resulting high correlation (r=0.888) between SOS and BMD at the same measurement site (66-68). However, BUA seems to depend more on the structural characteristics of trabecular bone (porosity, etc.) (67). In the case of SOS, the coefficient of variations (precision values) tend to be better in cortical bone compared to trabecular bone due to increased speed of sound waves in cortical bone. Similarly, BUA precision also appears to be poorer than its corresponding SOS precision in the same devices (60).

QUS possesses the main advantages of detecting different bone properties such as bone density, bone microarchitecture and elasticity (69). They are smaller, portable and cheaper than central DXA scanners, need no specially trained personnel, and do not use ionizing radiation.
radiation (70).

The aim of this narrative review is to examine in inflammatory rheumatic diseases whether (I) QUS could be used to correlate with BMD in terms of WHO criteria by DXA; (II) QUS could predict disease activity and its usefulness; and (III) QUS could predict fracture in these populations.

**QUS in inflammatory rheumatic diseases**

To examine these potential clinical utilities of QUS in inflammatory rheumatic diseases, the current narrative review was based on electronic database search, Medline and Embase via Ovid, covering a period from their respective inception until 30th September 2017. These databases were looked up individually for all possible terms (MeSH and key word), and the combination of terms to meet differences in their search engines. The terms used with Boolean operators “OR” for three search strategies were (I) osteoporosis and bone density; (II) QUS, ultrasound and ultrasonography; (III) rheumatic disease, inflammatory joint disease, inflammatory arthritis, rheumatoid arthritis, juvenile idiopathic arthritis, ankylosing spondylitis, systemic lupus erythematosus, psoriatic arthritis (PA), systemic sclerosis, polymyositis, dermatomyositis, Sjogren’s syndrome and vasculitis. Then the Boolean operator “AND” was used among the three results. Only original articles were included while excluding animal studies, review articles, case reports, publications focusing on surgery, sample size less than 25, and non-English papers. After screening titles and abstracts (n=230), and then full texts (n=83) for exclusion criteria, 34 articles were included in this narrative review. Of these, 13 papers examined the correlation of QUS with BMD; 22 papers evaluated the association of QUS with disease activity; 3 papers assessed the fracture prediction of QUS, as shown in the flow diagram (Figure 6).

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*Flow diagram of literature search. *, several papers examined more than one QUS utility. BMD, bone mineral density; RA, rheumatoid arthritis; JIA, juvenile idiopathic arthritis; AS, ankylosing spondylitis; SLE, systemic lupus erythematosus; PS, psoriatic arthritis; SS, systemic sclerosis.*
Rheumatoid arthritis (RA)

QUS association with BMD

In a sample of 51 RA patients, SOS of proximal phalanges was significantly correlated with lumbar spine, femoral neck and hand BMD, using DXA, \((r=0.49, 0.51 \text{ and } 0.72 \text{ respectively})\) (71). Calcaneal ultrasound demonstrated significant correlation of BUA with bone mineral content (BMC) and BMD \((r=0.6572, 0.6081, \text{ respectively})\), and of SOS with BMC and BMD \((r=0.4704, 0.4723)\) (72), suggesting the potential utility of QUS to evaluate BMD where DXA is unavailable.

In two separate case-control studies with 115 RA and 210 RA patients respectively, calcaneal QUS could discriminate between RA patients and controls better than DXA based on standardized response mean (73) and AUC \((\text{AUC } 0.67–0.68 \text{ for QUS, and AUC } 0.60–0.65 \text{ for DXA})\) (74), and between patients with and without vertebral deformities (74). The heel scan in 46 RA patients revealed a sensitivity of 90%, a specificity of 44% for a diagnosis of osteoporosis compared with DXA, a positive predictive value of 31% and a negative predictive value of 94%, suggesting the potential utility of heel ultrasound as a primary screening device (75). However, in the case of corticosteroid-induced osteoporosis, QUS did not appear to discriminate effects of corticosteroids on bone better than DXA in 76 RA patients (76).

In an interventional trial with 30 RA patients, AD-SoS values increased by 1.3% after 6 months of anti-TNF-\(\alpha\) treatment while BMD increased by 0.2% at the lumbar spine and 0.1% at the hip. On the contrary, the AD-SoS levels decreased by 4.6% during the same period in the untreated RA group while BMD decreased by 0.8% and 0.6% (at lumbar spine and the hip, respectively). This study might support that QUS could capture the effect of anti-TNF therapy on generalized and periarticular osteoporosis in RA patients (77). Long-term studies are required to answer the clinical importance/utility of this finding.

Relation of QUS to underlying disease characteristics

In 60 patients with RA, a significant reduction was detected in the Z scores with increased disease duration \((-1.52 \text{ vs. } -2.12, \ P=0.004)\), and the Z score for AD-SoS was lower in those with disease duration of less than 2 years \((-1.71)\) than in those with disease duration of 2–4 years \((-1.01)\) (78). A similar positive association between the severity of QUS osteoporosis at the calcaneus and symptom duration was reported in a larger sample \((n=256)\) (79). There existed an association between disease activity as determined by swollen joint and a combined swollen and tender joint and SOS, supporting the presence of a potentially adverse effect of clinically active disease on the bone (80).

The pronounced bone loss at the proximal phalanges of digits II–V was documented in patients with disease duration of 18–72 months (early RA) at the subchondral regions on measurements with SOS (81,82). However, discrepant results were published by Dragon et al. who determined failure of QUS parameters in 32 patients with early peripheral polyarthritis (median disease duration = 4 months) to classify these patients into RA or another rheumatic disease (83).

In a number of studies, RA patients using the finger ultrasound technique also failed to show a correlation between Z scores and disease activity markers such as ESR or CRP (71,78,84). Finger ultrasound was moderately correlated with measures of hand function, with correlation coefficients of 0.37 and 0.39 for health assessment questionnaires and grip strength (71).

QUS with fracture prediction

In a study \((n=825)\) which included a subset of RA patients (17%), QUS identified a higher number of women with increased fracture risk than the FRAX tool whose association was also relatively low, suggesting the incorporation of QUS parameters as an upgraded model of FRAX (85). Another study also reported an increased risk of fracture in patients with lower values of QUS (86).

Juvenile idiopathic arthritis

QUS association with BMD

A significant positive correlation \(r=0.54, P<0.001\) was detected between the lumbar DEXA and radius SOS \((n=40)\) (87). Spine and total body BMD measured by DXA correlated significantly with tibia SOS \((\text{spine: } r=0.57, P=0.007; \text{ total body: } r=0.68, P<0.001)\) in another study (88). Calcaneal BUA measurements were lower in the juvenile rheumatic patients compared with a control group \((P<0.001)\) and significantly correlated \((r=0.83)\) with lumbar spine BMD in a mixed sample of 29 RA, 13 SLE and 11 dermatomyositis patients, suggesting a probable application of QUS technique in estimating bone density in children (89).
A low bone mass and quality were detected in 151 patients with JIA compared to controls, and the normal bone condition was not obtained over time especially in children with polyarticular or systemic onset despite the current more effective drugs, potentially posing a high risk of osteoporosis in early adulthood (90).

**QUS with underlying disease characteristics**

One study documented improvement of bone QUS parameters in JIA after 1-year etanercept therapy which might be due to suppression of the underlying disease activity (91). A longitudinal study (n=166) followed up until puberty determined a significant negative association between AD-SoS, and systemic corticosteroids exposure or number of intra-articular corticosteroids injections, a positive association among TNF-alpha-blocking agents and AD-SoS, and no improvements in their QUS z-scores with respect to baseline (92). QUS parameters had a significant negative correlation with disease duration [(r=0.57 (BUA), r=0.67 (VOS)) and cumulative dose of prednisone [r=0.48 (BUA), r=0.50 (VOS)] in children with polyarticular JIA (93).

**QUS with fracture prediction**

There is a lack of studies examining the fracture prediction of QUS in this disease population.

**Ankylosing spondylitis**

**QUS association with BMD**

Weak to good correlations (r=0.22 to 0.53) were found between lumbar spine, femoral neck and total body BMD, and the different calcaneal QUS variables in 71 early AS patients (94). There was a significant correlation of calcaneal SOS with hip BMD (r=0.43) in 23 women with AS (95).

**QUS with underlying disease characteristics**

Calcaneal QUS parameters did not reveal significant association with variables of disease activities including ESR, serum CRP levels and BASDAI (94,95).

**QUS with fracture prediction**

In a study including 50 AS patients, increased calcaneal QUS, with a cut-off level T <-1.0 provided 70% sensitivity, 68% specificity, 35% positive predictive value and 90% negative predictive value, with femoral neck BMD. It might suggest the applicability of QUS to exclude severe osteoporosis (96). In the same study, it was reported that the sensitivity of QUS T <-1.0 to find the fractures was 80%, and the sensitivity of femoral neck DXA T score <=-2.5 was 60% (96).

**Systemic lupus erythematosus**

There is no study for QUS correlation with BMD and fracture prediction in the disease, which met our criteria.

**QUS with underlying disease characteristics**

In a case-control study in a mixed sample of SLE and RA patients (n=88), SOS but not BUA and DXA measurements reflected disease activities assessed by erythrocyte sedimentation rate (ESR) and CRP, suggesting that SOS might be more sensitive to alteration of bone secondary to the inflammation process and may reflect short-term bone status (97). In another study (n=43), young adults with SLE showed lower values of AD-SoS than controls, and had a low bone mass without catch-up growth over time, compared to healthy subjects, leading to a reduced final peak bone mass (98). Juvenile onset SLE patients had a reduced AD-SoS and QUS z-score (P<0.005) (99,100).

**Psoriatic arthritis**

No study exists for QUS correlation with BMD and fracture prediction in this disease.

**QUS with underlying disease characteristics**

Among psoriatic arthritis patients, reduced QUS parameters in at least one skeletal region were observed in 67% of premenopausal women, 100% of postmenopausal women, and 80% of the men. This was not related to the indices of inflammation or disease duration (101).

One study examined the responsiveness of QUS in a mixed sample of RA and PA (n=163), using clodronate (100 mg IM/week) with significant changes of QUS stiffness over 48 months (102).

**Systemic sclerosis**

Studies are lacking for QUS correlation with BMD and
fracture prediction in this disease.

**QUS with underlying disease characteristics**

In a cross-sectional study with 55 patients with systemic sclerosis, reduced BMD and SI was more marked in the diffuse form and in those with internal organ involvement. The QUS stiffness index was not related to inflammation indices, disease duration, or to the immunological pattern (103).

**Vasculitis**

No study exists for QUS correlation with BMD and fracture prediction in this disease.

**QUS with underlying disease characteristics**

Although significant reduction of AD-SoS was detected in RA patients, compared to the vasculitis and control groups, no significant difference existed between the latter groups despite the substantial glucocorticoid dose in vasculitis group. This finding might suggest that phalangeal QUS measurements are particularly suited to the study of bone destruction induced by immobilization or local inflammation rather than that induced by the detrimental effect of corticosteroid treatment (82).

**Limitations of QUS**

The major limitation of QUS in inflammatory rheumatic disease is the proliferation of various types of QUS scanners based on different ultrasound principles and applied to a variety of anatomical sites (104), utilizing different ultrasound mechanisms such as trabecular transverse transmission mostly measured at the heel, cortical transverse transmission used at the phalanges, cortical axial transmission applicable to the phalanges, radius and tibia (62,105). Therefore, it is inappropriate to directly compare measurements acquired with different QUS devices which are technologically different. The international consensus definition of osteoporosis and/or osteopenia using QUS variables is also still lacking.

In addition, most of the studies are focused on RA and JIA, and majority of these studies are not based on large population samples (<100 patients in most studies). Although the limited literature in these diseases demonstrated that QUS provided a substantial correlation with BMD, additional information in fracture prediction models and considerable diagnostic accuracy against BMD, further evidence is still required to be proposed as a diagnostic tool or screening instrument or combined fracture risk prediction model in these diseases (106). Regarding disease activities, QUS lacked significant correlation in most inflammatory diseases. Future studies based on large samples are required to demonstrate capability of QUS fracture prediction for these diseases, the ultimate goal of imaging in osteoporosis.

**Conclusions**

Bone mineral loss is a prevalent finding in inflammatory rheumatic diseases. Although QUS may have some complementary benefits to fracture risk prediction models, current literature does not support the substitution of QUS for DXA in the diagnosis and monitoring of osteoporosis in the rheumatic diseases. Most of the QUS studies are focused only on RA and JIA. In the case of RA, QUS has moderate to substantial correlation with DXA, a weak association with function and good discriminative validity between disease and control; however, the literature is conflicting in the use of early disease process, and corticosteroid-induced osteoporosis. In JIA, QUS parameters seem to improve after treatment with biologicals. To determine the utility of QUS in improving outcomes for osteoporotic rheumatic patients, future research is still required for evaluation of QUS clinimetrics as well as the cost-effectiveness of screening strategies that incorporate QUS in current fracture risk assessment tools.

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**Footnote**

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