Risk assessment for osteoporosis by quantitative ultrasound of the heel in ankylosing spondylitis

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Abstract

Objective

The aim of this cross-sectional cohort study is to assess the potential of quantitative ultrasound (QUS) of the calcaneus in pre-screening for vertebral/non-vertebral fractures, and in discriminating osteoporotic from normal bone density in patients with ankylosing spondylitis (AS); a second objective is to determine the prevalence of osteoporosis using dual-energy X-ray absorptiometry (DEXA) in this patient group.

Results

Included are 50 consecutive AS patients with no history of osteoporosis: mean (SD) age 52 (12) yrs, range 26-75 yr; female/male ratio 15/35. The mean (SD) DEXA T score in the lumbar spine (AP view) was -0.82 (1.73), mean (SD) DEXA T score in femoral neck -1.46 (1.12). The mean (SD) calcaneal QUS T score was -0.73 (0.95). In our population of AS patients the prevalence of femoral neck osteoporosis according to the WHO definition (DEXA T< -2.5) was 20%.

Osteoporosis criteria were met at the femoral neck in 10 (20%) patients, and 7 of them (70%) were correctly diagnosed using QUS, with T < -1.0 as cut-off value; normal bone density at the femoral neck was found in 15 AS patients (30%), yet in 2 of them the calcaneal QUS T was < -1.0. In AS the 20% pre-test probability of having femoral neck osteoporosis increased using calcaneal QUS, with a cut-off level T< -1.0 (70% sensitivity, 68% specificity), and then rose to 35% as the predictive value of a positive test, yielding a net result of QUS testing of +15%. The predictive value of a negative QUS test result was 90%, which makes QUS applicable to exclude severe osteoporosis. Vertebral and/or non-vertebral fractures occurred in 12 out of 50 AS patients (24%); 5 of them (10%) were associated with osteoporosis as defined by WHO criteria measured via DEXA.

Conclusion

The performance of QUS is similar to DEXA in finding patients with osteoporosis-associated fractures: the sensitivity of QUS T < -1.0 in finding the fracture is 80%, and the sensitivity of femoral neck DEXA T< -2.5 in finding fractured patients is 60%. We conclude that both osteoporosis and fractures are common sequelae in AS. Calcaneal QUS offers a promising approach to screen for osteoporosis, and may be applied to exclude osteoporosis-associated high fracture risk in AS.

Key words

Osteoporosis, osteopenia, fracture, ankylosing spondylitis (AS), quantitative ultrasound (QUS), DEXA.

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Introduction

Ankylosing spondylitis (AS) is a chronic disorder with inflammation of primarily the sacroiliac joints, spine and entheses, resulting in axial rigidity and deformation due to post-inflammatory extra-vertebral calcification as well as vertebral decalcification. Osteoporosis has long been considered a late and negligible feature of AS (1). However the loss of vertebral bone mass may occur already early in the course of AS (2, 3). Osteoporotic comorbidity is routinely screened for in only a minority of AS patients, as was recently demonstrated (4). Several years ago the World Health Organization (WHO) defined the golden standard for measuring bone density using dual-energy X-ray absorptiometry (DEXA). In AS however, measurement of axial bone density by DEXA is complicated due to specific disease-related axial changes. Therefore, DEXA evaluation of bone density in AS has its limitations with respect to the lumbar spine and femoral neck (5).

Bone status comprises not only of bone density, but also of bone structure. Alternative diagnostic techniques particularly measuring other aspects of bone status, such as quantitative ultrasound (QUS) may be of additional value in this patient group. Technically, QUS can be done at several peripheral bones: calcaneus, phalanges or tibia. For screening purposes of bone status, QUS of the heel is most promising, particularly since several studies have shown that calcaneal QUS provides a predictor of hip fracture risk. The majority of QUS studies have investigated post-menopausal women (6-10), and have focused on comparing healthy volunteers with fractured patients (6, 10, 11, 12). Correlations have been demonstrated between ultrasound parameters and age, duration of the post-menopausal period, height, weight, and the body mass index (7, 9, 13). Only few papers report on bone density in men (14-17). Data are scarce on the potential role of QUS for screening purposes in high-risk categories like patients with AS. We studied the potential role for QUS in screening for osteoporosis as defined by means of DEXA, and for increased fracture risk.

Materials and methods

Subjects

From July 1999 to July 2000, 50 consecutive AS patients gave their informed consent to undergo quantitative ultrasound measurements of the heel at two Rheumatology Outpatient Departments at secondary care, non-academic medical centres in Leeuwarden and Zwolle. Prior to inclusion patients were assessed clinically and biochemically. Laboratory tests included the erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), serum calcium, alkaline phosphatase (AP), 25-OH vitamin D, protein electrophoresis, and parathyroid hormone (PTH). Exclusion criteria were a history of hyperparathyroidism, thyroid gland disease, chronic liver or kidney disease, malignancy or malabsorption, and use of corticosteroids or thyroid hormones prior to inclusion in the study. Lumbar and pelvic X-rays were reassessed by a rheumatologist (TJ, SZ), in order to ascertain the diagnosis of lumbar fractures, and in order to verify the diagnosis of AS radiographically. SI joints were scored according to the modified New York criteria (grade I sacroiliitis = only discrete abnormalities, grade II = cortical loss without narrowing, grade III = cortical loss with narrowing, grade IV = cortical loss with narrowing and bridging) (18). Within 3 months after inclusion, bone densitometry was obtained in all patients.

Method

Evaluation of the skeletal status was based on QUS measurement of the dominant heel. The speed of sound (SOS, m/s) and broadband ultrasound attenuation (BUA, dB/MHz) were measured using the Sahara system (Hologic, Waltham, USA), calibrated in accordance with the manufacturer's recommendations. Corrections for the males regarding T score were done in accordance with the manufacturer's recommendations: subtraction of -0.6 from delivered T score.

Within a period of three months all

patients underwent measurement of bone density using dual-energy X-ray absorptiometry (DEXA) with Hologic (Waltham, Mass., USA) or Lunar (Madison, Wisc., USA) machines.

The WHO definitions for osteoporosis (DEXA T < -2.5) and osteopenia (DEXA T < -1.0 and T > -2.5) were used for stratification purposes.

Test characteristics

For calculation of the test characteristics, DEXA at the femoral neck was applied as the golden standard for osteoporotic disease, and the test QUS at the heel and DEXA at lumbar spine were applied. In consecutive testing fractures were applied as the golden standard and both QUS and DEXA values as test parameters.

The following test characteristics were then calculated: sensitivity (Se), specificity (Sp), predictive value of a positive test result (PPV), predictive value of a negative test result (NPV), and likelihood ratios (LR). An ideal test delivers both a high sensitivity and a high specificity (>95%) resulting in a high likelihood ratio of a positive test (LR+), theoretically ad infinitum: the ratio of the probability of obtaining a positive test result by applying the index test in diseased versus non-diseased subjects. The ratio of the probability of obtaining a negative test result in diseased versus non-diseased subjects ideally reaches zero: likelihood ratio of a negative test (LR-). A test is supposed to perform reasonably well when LR+ > 2.0, and LR- < 0.5.

Statistical analysis

All calculations have been carried out using SPSS 10.0 (Chicago, IL). Intraindividual DEXA T scores from lumbar spine (AP view) versus femoral neck are tested using Wilcoxon's non-parametric test. Analysis of associations between AS duration and ESR/bone density parameters are performed using linear logistic regression analysis. Pearson correlations are calculated; two-tailed p-values < 0.05 are accepted as significant.

Results

Included are 50 consecutive AS patients;

Table I. Characteristics of 50 consecutive patients with ankylosing spondylitis.

Female/male	15/35	
HLA B27 +	44	(88%)
Age (yr)	52	(12)
Duration AS (yr)	21	(13)
Weight (kg)	76.7	(12.6)
Body mass index (BMI) (kg/m^2)	30.5	(18.7)
Erythrocyte sedimentation rate (ESR) (mm/hr)	18	(14)
Sacroiliac (SI) score (0-4)	3.4 bilaterally	
Bamboo spine	36	(72%)
Squaring	9	(18%)
Fractures:	12	(24%)
Vertebral [lumbar spine (LS)]	3	(6%)
Non-vertebral	9	(18%)
Osteoporosis-associated	5	(10%)
Supposedly traumatic	7	(14%)

Data are means (SD) unless indicated otherwise

in 3 patients DEXA T scores of the lumbar spine were not reliable due to prosthetic material. Patient characteristics are given in Table I: 15 female, 35 male AS patients, mean (SD) age 52 (12) yr, mean SI score 3.5 (range: II-IV), bilaterally: 13 patients with grade II, 11 with grade III, and 26 with grade IV sacroiliitis. Previous fractures were found anamnestically and/or radiographically in 12 of the 50 AS patients (24%); vertebral fractures in lumbar spine in 3 patients (6%) probably due to osteoporosis; and non-vertebral fractures in 9 patients (18%).

Data were pooled with respect to the duration of AS: 12 patients had AS < 10 yrs; and 38 patients had AS with a duration exceeding 10 yrs. The HLA B27 allele was positive in 88%; for further details see Table I.

To evaluate potential bias of a mixing of the sexes, data between a patient group of both male and female AS (n = 50) and a group of exclusively male AS (n = 35) patients were compared. Intergroup comparison of bone density parameters did not reveal significant differences. This may serve as justification for the lumping procedure of sexes. Data are not demonstrated separately.

Prevalence of osteoporosis

In the lumbar spine and femoral neck, osteoporosis plus osteopenia (DEXA T

< -1.0) was demonstrated in the majority of AS patients with a respective prevalence of 54% and 72% (Table II). For osteoporosis (DEXA T < -2.5), the prevalence was 16% and 20%, respectively.

Intra-individual DEXA T scores from lumbar spine versus femoral neck showed significant intra-individual differences: mean DEXA T score (± SEM) at the lumbar spine was 0.23 (0.20) higher than at the femoral neck. The Pearson's correlation was 0.57 (p < 0.005).

Table II. Bone parameters of calcaneal quantitative ultrasonography (QUS) and dual-energy-X-ray absorptiometry (DEXA) in 50 patients with ankylosing spondylitis.

QUS$_{calcaneus}$		
Density$_{est}$ (gr/cm^2)	0.52	(0.12)
BUA (dB/MHz)	77	(17)
SOS (m/s)	1551	(31)
T score	-0.73	(0.95)
T < -1.0	40%	
DEXA T score:		
Lumbar spine	-0.82	(1.73)
T < -1.0	54%	
T < -2.5	15%	
Femoral neck	-1.46	(1.12)
T < -1.0	72%	
T < -2.5	20%	

Density$_{est}$ = estimated bone density. Data are means (SD).

Table III. Parameters of bone status in 50 patients with ankylosing spondylitis stratified according to the DEXA of the femoral neck: normal (T> -1.0) vs osteopenic (T> -2.5 and T< -1.0) vs osteoporotic (T< -2.5) bone density.

	Normal n=15		Osteopenia n=25		Osteoporosis n=10	
Age (yr)	46	(11)	51	(10)	64	(8)
Duration AS (yr)	15	(12)	23	(14)	25	(13)
ESR (mm/hr)	16	(9)	15	(11)	29	(19)
Fracture (n)	2	(13%)	6	(24%)	3	(30%)
DEXA T score						
LS (AP)	+0.19	(1.80)	-1.33	(1.66)	-1.31	(0.84)
FN	- 0.01	(0.53)	-1.67	(0.38)	-2.98	(0.37)
QUS$_{calcaneus}$						
Density$_{est}$ (gr/cm^2)	0.59	(0.05)	0.50	(0.11)	0.46	(0.13)
BUA (dB/MHz)	81	(17)	74	(16)	75	(19)
SOS (m/s)	561	(24)	1547	(29)	1550	(40)
Calcaneal T score	-0.15	(0.70)	-0.86	(0.91)	-1.21	(1.06)
T < -1.0	13%	*	44%	ns	70%	
T < -1.5	7%	*	28%	*	50%	
T < -2.0	0%	ns	20%	ns	40%	

Intergroup comparison of QUS T scores: ns: not significant; * P < 0.05.
Density$_{est}$: estimated bone density; fracture: prevalence of previous fractures; LS: lumbar spine; FN: femoral neck. Data are means (SD) unless stated otherwise.

Correlation

Linear regression analysis revealed a significant correlation between the duration of AS and the DEXA T score at the femoral neck (R=0.35, p<0.05), but not between the duration of AS and the DEXA T score at the lumbar spine (R=0.14, p>0.05).

Correlations were significant between the duration of AS and BUA (R=-0.57, p<0.001; CI [-0.54,-0.099]), and the duration of AS and SOS (R=-0.53, p< 0.005; CI [-0.89,-0.08]). Correlations were also signficant between QUS data and patient age: BUA, SOS and the QUS T score were correlated with the patient's age R=-0.48, p<0.05 with CI [-0.51, -0.08], -0.59, p<0.01 with CI [-0.62, -0.09] and -0.48, p<0.001 with CI [-8.9, -2.2] respectively. Ultrasonic BUA and SOS only just tended to be correlated with weight: the correlations were R=+0.35, p=0.08 with CI [-0.03, +0.50] and R =+0.24, p>0.1 with CI [-0.06,+0.25], respectively.

The QUS T score significantly correlateed with DEXA T scores from the lumbar spine and femoral neck: R=+0.45, p<0.005 with CI [+0.20, +1.0], and R=+0.48, p<0.002 with CI [+0.18, +0.76], respectively. SOS only just tended to correlate with femoral neck bone density.

Stratification according to femoral neck DEXA T scores

Patients were categorized according to their femoral neck DEXA T scores. Among 10 osteoporotic patients, 7 (70%) had a QUS T score < -1.0, whereas in the osteopenic group this was only 11 out of 25 patients (44%). In 15 AS patients the femoral neck DEXA T score was normal, but in 2 patients the QUS T score was < -1.0. For further details see Table III.

In 2 out of 15 AS patients (13%) with normal femoral neck DEXA T scores previous fractures were found: 1 vertebral in the lumbar spine and 1 non-vertebral. In 6 out of 25 osteopenic AS patients (24%) previous fractures were found: 2 vertebral fractures in lumbar spine and 4 non-vertebral fractures. In 3 out of 10 osteoporotic AS patients (30%) previous fractures were found: 1 vertebral in the lumbar spine and 2 non-vertebral fractures.

Test characteristics (Table IV)

QUS, performed at the dominant heel, predicted osteoporosis at the lumbar spine and femoral neck (cut off level T<-1.0) with a sensitivity of nearly 70% for both. Using a lowered QUS cut-off level of T< -1.5, the QUS test characteristics for osteoporosis screen-

ing hardly change.

Fracture risk: QUS T score > -1.0 was found in 30 out of 50 AS patients, yet in 6 of them (20%) previous fractures had occurred: the mean (SD) QUS T score was –0.22 (0.56). A QUS T score < –1.0 was found in 20 out of 50 AS patients, and in 5 of them (25%) previous fractures had occurred; the mean (SD) QUS T score was –1.84 (0.90)

The applicability of a screening test for osteoporosis in high risk populations depends on a high negative predictive value (NPV) in order to exclude disease, or on a high positive predictive value (PPV) in order to increase an individual's pre-test probability of having the disorder, i.e. osteoporosis. Table IV displays the PPVs of 2 QUS T score levels to find osteoporosis, and the PPVs of QUS T < -1.0 to find fractured patients (osteoporotic and/or supposedly traumatic) and osteoporosis-associated fractures. All PPVs demonstrated a limited additional value of the screening test: the PPVs attained never exceeded the pre-test probability by more than 25%. Contrarily, the NPVs revealed that QUS and DEXA are comparable in their clinical value to exclude fractures of any type and to exclude osteoporosis-associated fractures in particular: about 80% for both.

Nonetheless a reasonable test is obtained when QUS is applied at a cut-off level of T<1.0 in order to screen for lumbar spine and/or femoral neck osteoporosis. The DEXA approach to find osteoporosis-associated fractures as a test is non-informative, as the likelihood ratios do not reach the predefined levels of an acceptable test.

Discussion

Our study shows that many patients with ankylosing spondylitis (AS) have a significant loss of bone mass, as is reflected by a 50% prevalence of osteopenia and about 20% of osteoporosis. Of the 35 osteopenic and/or osteoporotic AS patients studied 9 (26%) had previous fractures, but only 3 had lumbar spine fractures. In our randomly assigned AS population still 10% had experienced previous fractures, associated with actual osteoporosis as defined by WHO criteria using

Table IV. Test characteristics of calcaneal QUS and DEXA (95% confidence intervals).

Test nr	P_{pre}	Se	Sp	PPV	NPV	LR+	LR-
cut-off level Sahara T < -1.0 **to screen for osteoporosis** (T < -2.5) at DEXA							
1. Lumbar spine T < -2.5	16%	75%	67%	30%	93%	2.25 (1.3-4.1)	0.38 (0.11-1.26)
2. Femoral neck T < -2.5	20%	70%	68%	35%	90%	2.15 (1.2-4.0)	0.45 (0.17-1.16)
cut-off level Sahara T < -1.5 **to screen for osteoporosis** (T < -2.5) at DEXA							
3. Lumbar spine T < -2.5	16%	63%	69%	28%	91%	2.02 (1.0-4.1)	0.54 (0.21-1.34)
4. Femoral neck T < -2.5	20%	50%	75%	33%	86%	2.00 (0.9-4.5)	0.67 (0.35-1.27)
to screen for fractured patients (12 cases out of 50)							
5. Femoral neck T < -2.5	24%	25%	82%	30%	78%	1.36 (0.4-4.5)	0.92 (0.6-1.3)
6. Calcaneal QUS T < -1.0	24%	42%	63%	26%	77%	1.14 (0.5-2.5)	0.92 (0.5-1.6)
to screen for osteoporosis-associated fractures (5 cases out of 50)							
7. Femoral neck T < -2.5	10%	60%	22%	8%	83%	0.77 (0.1-1.6)	1.80 (0.5-6.0)
8. Calcaneal QUS T < -1.0	10%	80%	44%	14%	95%	1.44 (0.9-2.3)	0.45 (0.1-2.7)

P_{pre} = pretest probability or prevalence; Se = sensitivity; Sp = specificity; PPV = predictive value of positive test result; NPV = predictive value of negative test result, LR+ = likelihood ratio of positive test, LR- = likelihood ratio of negative test.
Test numbers 1-4,6,8 reflect QUS as a screening test,and numbers 5,7 reflect DEXA as a screening test:a reasonable performance is obtained using tests 1 and 2.

DEXA T-scores. As bone status consists not only of bone density as measured by definition using dual energy X-ray absorptiometry, but also of bone structure more or less mirrored by ultrasonography, it seems plausible to expect that quantitative ultrasonography may have additional value in screening for patients prone to osteoporotic fractures.

A recent study by Bressant *et al.* showed that osteoporosis as a comorbidity of AS does not receive much attention from our British collegues despite the treatment options currently available (4). Previous studies already have demonstrated that comorbidity in AS is common, particularly with respect to osteopenia and osteoporosis both of which occur in 6-41% (19-22, 24, 25). These conditions indeed result in vertebral compression fractures in 9-16% (23). The present study is consistent with these data.

We hypothesized that clinically relevant bone strength may be mirrored by techniques such as quantitative ultrasonography, possibly even better than DEXA. In our population of AS patients QUS indeed was capable of retrieving 80% of the fractured patients associated with osteoporosis, whereas DEXA found 60%, which due to the number of patients included in the present study were percentages not significantly different from each other. As a test both QUS and DEXA perform reasonably well in the screening for osteoporosis as their likelihood ratios are similar. QUS may be slightly better than DEXA in screening for osteoporosis-associated fractures. And with respect to finding osteoporotic patients as defined by DEXA WHO criteria, QUS appears to find an additional part of the population at risk for fractures. This may suggest that QUS measures another factor involved in osteoporotic fracture risk, probably a factor of importance in bone quality as well.

Therefore, we conclude that quantitative ultrasound is quite applicable in a high risk population of patients with ankylosing spondylitis, i.e. to exclude an increased osteoporosis associated fracture risk in particular. An additional, though small, part of osteoporosis-associated fractures may be found which makes ultrasound probably equivalent to or perhaps even better in screening strategies to DEXA. Further prospective studies applying ultrasound in high risk populations are warranted.

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