

EXTENDED REPORT

Quantitative ultrasound and bone mineral density: discriminatory ability in patients with rheumatoid arthritis and controls with and without vertebral deformities

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Ann Rheum Dis 2004;**63**:945–951. doi: 10.1136/ard.2003.010819

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Accepted
28 September 2003

Background: Quantitative ultrasound (QUS) is a reliable tool for discriminating between subjects with and without vertebral deformities in postmenopausal osteoporosis. Less is known about osteoporosis caused by inflammatory diseases or corticosteroid use.

Objectives: (1) To compare in patients with rheumatoid arthritis the ability of QUS and dual energy x ray absorptiometry (DXA) to discriminate between those with and without vertebral deformities; (2) to explore whether the results are similar in population based controls.

Methods: Standardised lateral radiographs of the spine were obtained from 210 patients with rheumatoid arthritis aged over 50 years and 210 individually matched controls. Vertebral deformities were assessed morphometrically and semiquantitatively. All participants underwent bone measurements by DXA (Lunar Expert) and QUS (Lunar Achilles+). Receiver operating curve (ROC) analysis was used to compare the discriminating ability of BMD and QUS measurements in patients and controls with and without vertebral deformities. Analyses were repeated in patients stratified according to corticosteroid use.

Results: For all bone measurements except lumbar spine in the rheumatoid arthritis group, BMD discriminated significantly between the patients with and without vertebral deformities, and the results were similar to those obtained in controls. Among current corticosteroid users, neither QUS nor DXA could discriminate between subjects with and without vertebral deformities.

Conclusions: These findings support QUS as an alternative tool for identifying patients at risk of having vertebral deformities in rheumatoid arthritis, although results should be interpreted with caution in current users of corticosteroids.

Patients with rheumatoid arthritis have an increased risk of both vertebral and hip fractures.^{1–4} This is partly attributable to low bone mineral density (BMD) as measured by dual energy x ray absorptiometry (DXA).^{1–5} Rheumatoid arthritis is one of the most common chronic inflammatory diseases, often requiring the use of corticosteroids. Although effective in suppressing symptoms and modifying disease progression,⁶ long term use or higher doses are associated with various side effects including osteoporosis and an increased fracture risk. Some studies have suggested that other bone related factors than those reflected by BMD might contribute to the excess fracture risk in rheumatoid arthritis or in patients using corticosteroids.^{3–7} Previous research has been inconclusive, but a recent thorough review concluded that the cumulative evidence points towards an increased fracture risk in corticosteroid users independently of BMD.⁸ Additionally, quantitative computed tomography of the spine was found to be a better predictor of vertebral deformities in corticosteroid induced osteoporosis than DXA, reflecting the fact that other methods can give additional information about fracture risk.⁹

Several studies on postmenopausal osteoporosis have established that quantitative ultrasound (QUS) indices discriminate significantly between subjects with and without vertebral deformities,^{10–12} as well as predicting fractures in prospective studies.^{13–15} The relation between QUS variables and vertebral deformities in patients with rheumatoid arthritis and in those requiring corticosteroids has been explored to a limited extent only,^{16–19} especially for fracture discrimination.

The calcaneus is rich in trabecular bone, which is more responsive to corticosteroid induced osteoporosis than cortical bone.^{20–21} Quantitative ultrasound (QUS) also appears to provide information on bone microarchitecture in addition

to density,^{22–24} and could be especially applicable in patients with increased fracture risk attributed to reduced bone quality.¹⁷ Additionally, QUS devices have several advantages over DXA machines, being portable, relatively inexpensive, radiation-free, and easy to use, thus representing an attractive alternative to DXA if providing the same or better information about fracture risk.

In a smaller group of patients we have previously shown that QUS and DXA measurements were reduced in patients with rheumatoid arthritis compared with controls.²⁵ Furthermore, this previous study showed that BMD of the total hip and femoral neck and all QUS variables were independently related to cumulative disease activity measured as the 18 deformed joints count.

Our aim in the present study was to compare the ability of QUS and DXA measurements to discriminate between rheumatoid patients with and without vertebral deformities in a large cohort, and to compare the results with those obtained in population based controls. Separate analyses were undertaken among current users and non-users of oral corticosteroids.

METHODS

The 210 patients with rheumatoid arthritis included in this study were recruited from the Oslo rheumatoid arthritis register (ORAR). The ORAR consists of patients fulfilling the American College of Rheumatology (ACR) 1987 revised

Abbreviations: ACR, American College of Rheumatology; BMD, bone mineral density; BUA, broadband ultrasound attenuation; DAS, disease activity score; DXA, dual energy x ray absorptiometry; ORAR, Oslo rheumatoid arthritis register; QUS, quantitative ultrasound; SI, stiffness index; SOS, speed of sound

Table 1 Demographic and disease characteristics for patients with rheumatoid arthritis and controls, and for rheumatoid arthritis patients stratified according to current use of corticosteroids

| Variable | Comparison of patients and controls | | | Comparison of patients stratified according to current corticosteroid use | | |
|---------------------------|-------------------------------------|------------------|----------|---|------------------|----------|
| | Patients (n=210) | Controls (n=210) | p Value* | Patients (n=210) | Controls (n=210) | p Value† |
| Age (years) | 63.0 (6.7) | 63.4 (6.7) | <0.001 | 63.9 (6.4) | 62.2 (7.0) | 0.08 |
| Height (cm) | 164.3 (5.9) | 163.7 (5.9) | 0.29 | 164.2 (6.0) | 164.5 (6.8) | 0.68 |
| Weight (kg) | 66.7 (12.2) | 69.2 (11.2) | 0.03 | 68.0 (13.2) | 65.6 (11.3) | 0.17 |
| BMI (kg/m ²) | 24.7 (4.4) | 25.8 (4.1) | 0.008 | 25.2 (5.0) | 24.2 (3.9) | 0.10 |
| Disease duration (years) | 16.1 (10.0) | | | 17.7 (10.3) | 14.7 (9.6) | 0.03 |
| RF positive (%) | 51.7 | | | 64.5 | 40.7 | <0.001 |
| 28-DAS | 4.71 (1.24) | | | 5.15 (1.18) | 4.34 (1.18) | <0.001 |
| MHAQ | 1.65 (0.55) | 1.11 (0.25) | <0.001 | 1.84 (0.59) | 1.48 (0.45) | <0.001 |
| 18 deformed joints count | 4.23 (5.0) | | | 5.6 (5.3) | 3.0 (4.3) | <0.001 |
| Smoking status | | | | | | |
| Current smoker | 32.4 | 27.5 | 0.40 | 34.7 | 30.3 | 0.50 |
| Ever smoked | 64.2 | 54.2 | 0.08 | 67.3 | 62.4 | 0.46 |
| Current DMARD use (%) | 55.4 | | | 62.2 | 39.3 | <0.001 |
| Corticosteroid use | | | | | | |
| Current user (%) | 46.7 | 1.9 | <0.001 | 100 | 0 | |
| Ever used (%) | 69.5 | 10.0 | <0.001 | 100 | 40.2 | <0.001 |
| Long term use‡ | 51.9 | 1.9 | <0.001 | 90.8 | 17.9 | <0.001 |
| Bone protecting agents | | | | | | |
| Oestrogens | | | | | | |
| Current user (%) | 42.6 | 30.0 | 0.02 | 45.4 | 40.2 | 0.45 |
| Ever used (%) | 58.4 | 49.8 | 0.10 | 60.8 | 56.3 | 0.55 |
| Bisphosphonates | | | | | | |
| Current user (%) | 10.6 | 1.4 | <0.001 | 16.5 | 5.4 | 0.009 |
| Ever used (%) | 14.4 | 1.9 | <0.001 | 21.6 | 8.0 | 0.005 |
| Calcitonin | | | | | | |
| Current user (%) | 1.0 | 1.0 | 1.00 | 2.3 | 0 | 0.19 |
| Ever used (%) | 4.0 | 1.4 | 0.22 | 8.0 | 0.9 | 0.01 |
| Calcium supplementation | | | | | | |
| Current user (%) | 62.4 | 20.0 | <0.001 | 81.1 | 46.4 | <0.001 |
| Ever used (%) | 74.6 | 25.8 | <0.001 | 90.5 | 60.9 | <0.001 |
| Vitamin D supplementation | | | | | | |
| Current user (%) | 72.8 | 56.7 | <0.001 | 86.0 | 61.5 | <0.001 |
| Ever users (%) | 81.7 | 65.9 | <0.001 | 92.5 | 72.5 | <0.001 |

Values are mean (SD) for continuous variables, % for counts.

*Paired analyses, *t* tests for continuous variables and McNemar's tests for dichotomous variables.

†Group comparisons, unpaired *t* tests for continuous variables and χ^2 tests for dichotomous variables.

‡Ever used for 12 months or more.

BMI, body mass index; DAS, disease activity score; DMARD, disease modifying antirheumatic drugs; MHAQ, modified health assessment questionnaire.

classification criteria for rheumatoid arthritis.²⁶ The completeness of the register has been reported to be 85%, and it has been described in detail previously.²⁷ Patients and controls were recruited from a study of the frequency of vertebral deformities in rheumatoid arthritis.^{1, 28} Each subject had anteroposterior and lateral radiographs taken according to a standardised procedure. Vertebral deformities were analysed morphometrically, applying the McCloskey algorithm²⁹ for the identification of vertebral deformities. Briefly, measurements of the anterior (A), central (C), and posterior (P) vertebral heights were captured using a semiautomated technique comprising a backlit digitising tablet and a computer database. The definition of deformity requires the fulfilment of two criteria for each of the three vertebral height ratios (A/P, C/P, and P/Predicted P) with at least one ratio reduced to more than 3 SD below their expected mean values. In addition, all radiographs were analysed semi-quantitatively by an experienced radiologist, applying the method described by Genant *et al.*³⁰ Deformed vertebrae were classified as grade 1 (mild), grade 2 (moderate), or grade 3 (severe), representing a reduction in any of the vertebral heights of 20–25%, 25–40%, and more than 40%, respectively.

BMD measurements of the hip (whole hip and femoral neck) and the lumbar spine (L2–4, anterior-posterior) were made using the same DXA equipment (Lunar Expert, Madison, Wisconsin, USA). T and Z score estimations were computed from a pooled European/US reference database. Descriptions of the reference database, equations for

computing age and weight adjusted Z score estimations, and quality control procedures have been published previously.⁵

QUS assessment of both heels using the same Achilles Plus device (Lunar) was undertaken on all participants.²⁵ Broadband ultrasound attenuation (BUA) and speed of sound (SOS) were measured, as well as a stiffness index ($SI = 0.67 \cdot BUA + 0.28 \cdot SOS - 420$), an index established by Lunar which should not be confused with the biometrical term.³¹ In five patients and six controls only one foot was measured; otherwise the mean of the two values was calculated and used in the statistical equations. T and Z scores for SI were computed from an American reference database using the following equations:

$$T \text{ score} = (SI - 100)/16$$

$$Z \text{ score} = (SI - \text{age matched mean SI})/16,$$

where age matched mean $SI = 68 + 31.6/(1 + (\text{age}/55.9) \cdot 10.1)$ ³²

For the in vivo precision (CV%) calculation for the QUS measurements ($CV\% = \{(\sum D^2/2N)/\text{mean}\}^{**}100$), 10 healthy hospital workers were measured twice two days apart by each of the six technicians involved in the study. The overall in vivo precision including all measurements in the analysis was for SOS 1.0%, for BUA, 4.5%, and for SI 4.7%. The in vivo short term precision for each of the six technicians measuring the same 10 healthy hospital workers ranged from 0.3% to 1.7% for SOS, from 2.3% to 6.9% for BUA, and from 2.9% to 6.7% for SI.

Demographic, patient, and disease characteristics, including conventional rheumatoid arthritis disease core measurements (table 1), were recorded partly by self reported questionnaires and partly by interview and clinical examination. Joint assessment included a 28 swollen joint count, a 28 tender joint count, and an 18 deformed joint count. The disease activity score (DAS) was computed using a 28 joint count. Patients having a rheumatoid factor (RF) titre of ≥ 64 measured on at least one occasion during the disease course were considered to be RF positive. Details of these measurements have been published previously.²⁸

Data analyses and statistics

Group comparisons were done applying paired tests when appropriate (patients versus controls) or unpaired tests (steroid users versus non-users). The same simple logistic regression analysis was applied for both patients and controls to compute risk estimates (odds ratios (OR)) for vertebral deformities according to a 1 SD T score reduction for the different bone variables, and a multivariate stepwise model to explore which variable was selected as the most informative for the two groups. Receiver operating curve (ROC) analysis was then applied to compare the ability of QUS and DXA to discriminate between subjects with and without vertebral deformities. ROC curve analysis takes into account the sensitivity and specificity of the method in question, and the null hypothesis is that the area under the curve is 0.5. We then applied the equations for comparing areas under the curve (AUCs) described by Hanley and McNeil,³³ to explore whether there was a significant difference between the AUCs derived from the bone variables in each group. All analyses were undertaken with the SPSS (Statistical Package for Social Sciences) program, version 11.0 (SPSS, Chicago, Illinois, USA). Probability (p) values ≤ 0.05 were considered significant.

RESULTS

Characteristics of patients and controls

Demographic and clinical characteristics of patients and controls are listed in table 1. There was a numerically small, but statistically significant, difference in age between patients and controls. Other group differences of importance were found for body weight, body mass index (BMI), disability level, use of corticosteroids, and drug treatment for osteoporosis.

Ninety eight patients (46.7%) were current users of corticosteroids. These patients had significantly longer disease duration and were more disabled than current non-users (table 1). Current steroid users were also more likely to be RF positive. There were no significant differences between the groups for age, height, weight, smoking status, or oestrogen use. Significantly more patients in the corticosteroid group were, however, current users of other bone protecting agents (mainly bisphosphonates).

There was a significant difference between patients and controls for all DXA and QUS variables. Among the rheumatoid group, current steroid users had lower BMD and QUS values than non-users at all measurement points (table 2).

The total number of vertebral deformities assessed morphometrically was 110 in the rheumatoid group and 43 in the control group. Forty six patients (21.9%) and 31 controls (14.6%) had one or more vertebral deformity (OR 1.79, 95% confidence interval (CI), 0.99 to 3.32). Twenty two (10.5%) versus 10 (4.5%) had multiple deformities (OR 2.50, 95% CI 1.10 to 6.56). In the subgroup analysis, 70 of the total of 110 deformities were found among the 98 current corticosteroid users. The numbers of patients having deformities among users versus non-users of corticosteroids were 27 (27.1%) v 19

(17.0%) for any deformity, and 15 (15.3%) v 7 (6.3%) for multiple deformities (OR (95% CI), 1.86 (0.95 to 3.61) and 2.71 (1.06 to 7.0), respectively).

Relation between bone variables and vertebral deformities

Table 3 gives mean values for all six bone measurements for patients and controls with and without vertebral deformities. There was a significant difference for all variables in the rheumatoid arthritis group. In the control group, the differences for whole hip BMD and SOS were of borderline significance only ($p = 0.06$ and 0.07 , respectively). When repeating the analyses in the patient group controlling for current and long standing disease activity (DAS and the 18 deformed joints count) and disability (modified health assessment questionnaire (MHAQ)), the results were unaltered (OR (95% CI) for BMD at the femoral neck was 1.64 (1.12 to 2.4); for total hip, 1.72 (1.18 to 2.5); for BMD at the spine, 1.23 (0.98 to 1.55); and for SI 1.98 (1.32 to 3.00)).

Table 4 gives odds ratios per 1 SD T score reduction for any vertebral deformity in patients and controls. Odds ratios were generally higher for rheumatoid patients than controls, and higher for SI than for the different DXA variables. When all six bone measurements were analysed together by stepwise logistic regression, SI was selected as the preferred variable for both rheumatoid patients (OR (95% CI), 1.84 (1.31 to 2.57)) and controls (OR 1.57 (1.06 to 2.33)).

In ROC curve analysis, all bone variables except BMD at the spine could discriminate significantly between rheumatoid arthritis patients with and without vertebral deformities (table 5A and 5A). In the control group, the areas under the curves were generally smaller than in the rheumatoid group, but significant for all variables except BMD at the total hip. The DXA and QUS measurement with the highest AUCs were then compared according to the method described by Hanley and McNeil,³³ both in the rheumatoid group and the control group. There was no significant difference between the AUCs for neither rheumatoid arthritis patients or controls (rheumatoid patients $Z = 0.72$, $p = 0.47$, controls $Z = 0.71$, $p = 0.48$).

Comparing patients according to current steroid use

Table 6 shows BMD values in patients with and without vertebral deformities, stratified according to corticosteroid use. In patients who were current steroid users, the difference in BMD values between those with and without vertebral deformities was not significant, though all the QUS variables gave significant differences. When applying Z scores, the difference in bone status was almost negligible among current corticosteroid users, especially for SI (fig 1B). In non-users, all bone measurements were significantly different between the groups.

The AUCs were generally larger in the non-corticosteroid group, where all variables except BMD at the spine could discriminate significantly between subjects with and without any vertebral deformity (table 7A and 7B). Among current users, the AUCs for the QUS variables were larger than the DXA variables, but their ability to discriminate between patients with and without vertebral deformities was only of borderline significance.

DISCUSSION

In this study of 210 female patients with rheumatoid arthritis and matched controls, QUS proved to be at least as reliable as DXA in identifying patients with vertebral deformities. The relation between bone measurements and vertebral deformities was more pronounced in patients with rheumatoid arthritis than in population based controls. In both groups, QUS (stiffness index) was the measurement method

Table 2 Bone variables for rheumatoid arthritis patients and controls, and for rheumatoid arthritis patients stratified by current use of corticosteroids

| | Comparison of patients and controls | | | Comparison of patients stratified according to current corticosteroid use | | |
|---------------------------------------|-------------------------------------|--------------------|----------|---|---------------------|----------|
| | Patients (n = 210) | Controls (n = 210) | p Value* | Users (n = 98) | Non-users (n = 112) | p Value† |
| BMD femoral neck (g/cm ²) | 0.81 (0.14) | 0.88 (0.11) | <0.001 | 0.78 (0.12) | 0.83 (0.14) | 0.02 |
| BMD total hip (g/cm ²) | 0.84 (0.15) | 0.91 (0.13) | <0.001 | 0.80 (0.14) | 0.86 (0.15) | 0.003 |
| BMD L2–L4 (g/cm ²) | 1.05 (0.20) | 1.11 (0.20) | <0.001 | 1.01 (0.17) | 1.09 (0.21) | 0.001 |
| SOS (m/s) | 1484.9 (34.6) | 1519.3 (35.7) | <0.001 | 1476.5 (36.0) | 1492.2 (31.7) | 0.001 |
| BUA (dB/MHz) | 98.9 (14.5) | 110.5 (13.2) | <0.001 | 95.3 (13.7) | 102.0 (14.5) | 0.001 |
| SI | 61.7 (18.5) | 79.0 (17.6) | <0.001 | 57.0 (18.4) | 65.8 (17.7) | 0.001 |

Values are mean (SD).

*Paired analyses, *t* tests for continuous variables and McNemar's tests for dichotomous variables.

†Group comparisons, unpaired *t* tests for continuous variables and χ^2 tests for dichotomous variables.

BMD, bone mineral density; BUA, broadband ultrasound attenuation; SI, stiffness index; SOS, speed of sound.

with the highest AUC. However, in the subgroup of rheumatoid patients who were current corticosteroid users, we found no significant differences in BMD for any measurement point between patients with and without any vertebral deformity, but significant differences in the QUS variables SOS and stiffness index.

Previous studies on the applicability of QUS in corticosteroid induced osteoporosis have focused on the differences in DXA and QUS variables between patients and controls. In two studies, there was a discrepancy in mean reduction between patients and controls with respect to QUS and DXA measurements.^{17–18} However, in the study by Blancaert *et al*,¹⁶ QUS measures were reduced to the same extent (SOS –1.6%; BUA –6.3%; SI –15.8%) as the DXA measurements. In a previous publication on a subset of 115 patients with rheumatoid arthritis from our own department, we found that QUS discriminated better than DXA between patients and controls on a group level.²⁵

Only one previous study on QUS including only patients with rheumatoid arthritis compared subjects with and without vertebral deformities. Among 76 patients, Sambrook *et al*¹⁹ found a significant difference in femoral, but not lumbar, BMD and for three QUS variables (McCue CUBA II) in the 11 patients with any vertebral deformity compared with those without. The findings were the same in the sample as a whole and in a subset of 40 patients currently using low dose corticosteroids. No comparisons with controls were done in that study.¹⁹

In the control group, the relation between vertebral deformities and both DXA variables and QUS was rather weak (tables 3 and 4B) compared with a recently published

study on the discriminatory effect of QUS in postmenopausal osteoporosis.¹¹ However, the subjects in the latter study were older, and a strong relation between bone variables and deformities was shown for no deformities versus multiple deformities only. Our study was not powered to do separate analyses on subjects with multiple deformities in the control group, as the numbers were small. Similarly, the more pronounced differences in bone variables between subjects with and without vertebral deformities in the rheumatoid arthritis group compared with the controls could reflect differences in the magnitude of vertebral osteoporosis.

Our study clearly shows that QUS is as predictable as DXA in discriminating between rheumatoid patients with and without vertebral deformities, and suggests that it could even be better. However, the differences between the AUCs in the ROC curve analysis were rather small and non-significant. Thus any difference between QUS and DXA is unlikely to have important clinical implications. The relative differences in fracture discrimination appear comparable in rheumatoid patients and controls. It is unlikely that QUS gives any complementary information on fracture status in rheumatoid arthritis that differs from that seen in postmenopausal osteoporosis.

It is more difficult to explain the striking differences between the patients who were and were not current corticosteroid users. For the last decade, it has been debated whether fractures in rheumatoid arthritis and corticosteroid induced osteoporosis are dependent on BMD to the same extent as in postmenopausal osteoporosis. The dispute started with an article by Luengo *et al* on patients with obstructive pulmonary disease.⁷ They found that the

Table 3 Bone variables in patients and controls with and without any vertebral deformity, measured morphometrically

| | Rheumatoid arthritis | | p Value | Controls | | p Value |
|---------------------------------------|----------------------|---------------|---------|---------------|---------------|---------|
| | Any VD (46) | No VD (166) | | Any VD (31) | No VD (179) | |
| <i>DXA variables</i> | | | | | | |
| BMD femoral neck (g/cm ²) | 0.75 (0.14) | 0.82 (0.13) | 0.004 | 0.83 (0.13) | 0.88 (0.12) | 0.04 |
| T score | –1.9 | –1.3 | | –1.3 | –0.8 | |
| BMD total hip (g/cm ²) | 0.77 (0.14) | 0.85 (0.14) | 0.002 | 0.87 (0.13) | 0.92 (0.13) | 0.07 |
| T score | –1.9 | –1.2 | | –1.4 | –0.7 | |
| BMD L2–L4 (g/cm ²) | 0.99 (0.20) | 1.07 (0.19) | 0.02 | 1.04 (0.19) | 1.12 (0.20) | 0.03 |
| T score | –1.7 | –1.1 | | –1.35 | –0.66 | |
| <i>QUS variables</i> | | | | | | |
| SOS m/s | 1467.8 (34.3) | 1489.7 (33.2) | <0.001 | 1508.3 (40.7) | 1521.2 (34.4) | 0.06 |
| BUA dB/MHz | 91.4 (14.7) | 101.0 (13.8) | <0.001 | 105.4 (14.2) | 111.5 (12.9) | 0.02 |
| Stiffness index | 52.0 (18.7) | 64.4 (17.5) | <0.001 | 72.5 (20.1) | 80.2 (19.9) | 0.02 |
| T score | –3.0 | –2.2 | | –1.7 | –1.2 | |

Values are mean (SD) for continuous variables, and mean T scores when available, see text for details.

BMD, bone mineral density; BUA, broadband ultrasound attenuation; SOS, speed of sound; VD, vertebral deformity.

Table 4 Odds ratios for any vertebral deformity per 1 SD T score reduction of various bone measurements in rheumatoid arthritis patients and controls

| | Patients | | Controls | |
|------------------|----------|--------------|----------|--------------|
| | OR | 95% CI | OR | 95% CI |
| BMD femoral neck | 1.58 | 1.14 to 2.20 | 1.48 | 1.01 to 2.18 |
| BMD total hip | 1.63 | 1.19 to 2.22 | 1.40 | 0.96 to 2.03 |
| BMD L2-L4 | 1.29 | 1.04 to 1.61 | 1.32 | 1.03 to 1.71 |
| Stiffness index | 1.87 | 1.36 to 2.58 | 1.54 | 1.04 to 2.28 |

BMD, bone mineral density; CI, confidence interval; OR, odds ratio.

threshold for vertebral fractures in patients receiving a mean of 12 mg prednisolone daily was significantly higher than in patients with postmenopausal osteoporosis. Later, Peel *et al* found a sixfold increase in vertebral deformity rate in corticosteroid users compared with controls, but only a 0.79 SD reduction in lumbar spine BMD.³ Furthermore, there was no significant difference in lumbar spine BMD in the rheumatoid arthritis group between patients with and without prevalent vertebral deformities. Later studies, such as one by Selby *et al*,³⁴ have concluded differently and stated that BMD is also a main predictor of fractures in corticosteroid induced osteoporosis.³⁴ In a recent thorough review, however, van Staa *et al* concluded that the BMD threshold in corticosteroid induced osteoporosis is probably different from in postmenopausal osteoporosis.⁸

When accounting for the magnitude of deformities in rheumatoid patients and controls in our own study on vertebral deformities in rheumatoid arthritis, we found that a diagnosis of rheumatoid arthritis and long term corticosteroid use were both predictors of vertebral deformities independently of BMD.¹ In the present analysis, we wanted to explore this further by analysing the patients according to corticosteroid use, and add information on QUS. Patient who were current steroid users had significantly lower values for all bone variables than current non-users (table 1). However, it seems that BMD could not discriminate between subjects with and without vertebral deformity among current corticosteroid users. The number of patients in the groups was similar, and there were more deformities in the corticosteroid group, so the results could not reflect to lack of statistical power.

The reason for our findings could be that corticosteroids induce rapid BMD loss, so that patients who were not previously osteoporotic had developed a low BMD but had not yet had fractures. A second reason could be that when a certain BMD threshold had been reached, other risk factors such as bone quality (not captured by QUS) or age were more important in determining which patients develop fractures. The latter is supported by the age adjusted Z scores presented in fig 2B, where no differences were seen (either for BMD at the whole hip or for SI) between patients with and without vertebral deformities among current steroid users.

Clinicians are aware of osteoporosis in patients receiving corticosteroids and are thus likely to prescribe treatment to prevent bone loss. Indeed, significantly more patients in the corticosteroid group than in the non-corticosteroid group used bone protecting agents other than oestrogens (mostly bisphosphonates, see table 1), especially those with vertebral deformities. If the comparative analysis leading to the results shown in fig 2 included adjustments for present and accumulated disease activity, disability, and the use of oestrogens and bisphosphonates, neither of the measurements could discriminate significantly between subjects who were current corticosteroid users: the mean difference for the

Table 5 Area under the curve for bone measurements for patients with rheumatoid arthritis and controls

| | AUC | SE | 95% CI |
|--|------|------|--------------|
| <i>(A) Rheumatoid arthritis patients</i> | | | |
| BMD femoral neck (g/cm ²) | 0.64 | 0.06 | 0.55 to 0.73 |
| BMD total hip (g/cm ²) | 0.65 | 0.05 | 0.56 to 0.74 |
| BMD L2-L4 (g/cm ²) | 0.60 | 0.05 | 0.50 to 0.69 |
| SOS (m/s) | 0.67 | 0.05 | 0.58 to 0.76 |
| BUA (dB/MHz) | 0.67 | 0.05 | 0.58 to 0.76 |
| Stiffness index | 0.68 | 0.05 | 0.59 to 0.77 |

| | | | |
|---------------------------------------|------|------|--------------|
| <i>(B) Controls</i> | | | |
| BMD femoral neck (g/cm ²) | 0.61 | 0.05 | 0.50 to 0.72 |
| BMD total hip (g/cm ²) | 0.60 | 0.06 | 0.49 to 0.71 |
| BMD L2-L4 (g/cm ²) | 0.63 | 0.06 | 0.52 to 0.75 |
| SOS (m/s) | 0.63 | 0.06 | 0.52 to 0.75 |
| BUA (dB/MHz) | 0.64 | 0.06 | 0.53 to 0.75 |
| Stiffness index | 0.64 | 0.06 | 0.53 to 0.75 |

AUC, area under the curve; BMD, bone mineral density; BUA, broadband ultrasound attenuation; CI, confidence interval; OR, odds ratio; SE, standard error; SOS, speed of sound.

whole hip Z score in current users was -0.20 ($p = 0.42$) and in non-users, 0.68 ($p = 0.006$); the corresponding values for SI Z score were -0.13 ($p = 0.53$) and 0.68 ($p = 0.003$).

Raw values of BUA and SI measurements were significantly different in corticosteroid using patients with and without vertebral deformities. This indicates that QUS could be a better tool for identifying individuals with vertebral deformities among patients currently on steroid treatment, perhaps reflecting bone quality. Applying ROC curves,

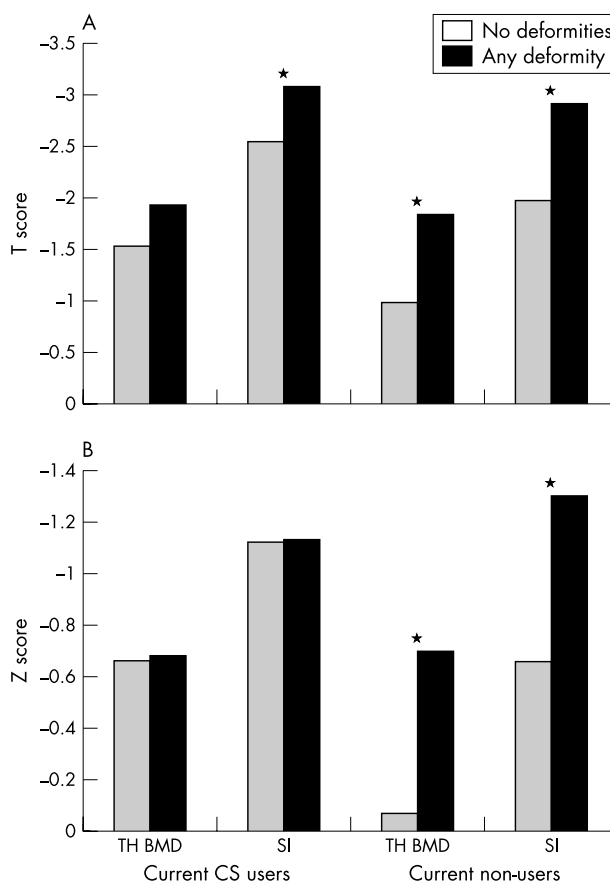
**Figure 1** (A) Patients with and without any vertebral deformity stratified by corticosteroid use (T scores). (B) Patients with and without any vertebral deformity stratified by corticosteroid use (Z scores).

Table 6 Bone measurements in rheumatoid arthritis patients with and without any vertebral deformity measured morphometrically, stratified according to current corticosteroid use

| | Current corticosteroid users (n = 98) | | | Non-users (n = 112) | | |
|---------------------------------------|---------------------------------------|---------------|---------|---------------------|---------------|---------|
| | Any VD (27) | No VD (67) | p Value | Any VD (19) | No VD (93) | p Value |
| <i>BMD variables</i> | | | | | | |
| BMD femoral neck (g/cm ²) | 0.75 (0.11) | 0.79 (0.12) | 0.17 | 0.75 (0.17) | 0.84 (0.13) | 0.02 |
| T score | -1.9 | -1.6 | | -1.9 | -1.2 | |
| BMD total hip (g/cm ²) | 0.77 (0.14) | 0.82 (0.13) | 0.17 | 0.78 (0.16) | 0.88 (0.14) | 0.006 |
| T score | -1.9 | -1.5 | | -1.8 | -1.0 | |
| BMD L2-L4 (g/cm ²) | 0.99 (0.16) | 1.01 (0.19) | 0.50 | 1.00 (0.23) | 1.11 (0.20) | 0.04 |
| T score | -1.8 | -1.5 | | -1.6 | -0.7 | |
| <i>QUS variables</i> | | | | | | |
| SOS (m/s) | 1464.5 (35.2) | 1481.1 (35.5) | 0.04 | 1472.5 (33.4) | 1496.2 (30.0) | 0.003 |
| BUA (dB/MHz) | 91.2 (15.0) | 96.9 (13.0) | 0.07 | 91.8 (14.7) | 104.1 (13.5) | 0.001 |
| Stiffness index | 51.0 (19.4) | 59.3 (17.7) | 0.04 | 53.6 (18.3) | 68.3 (16.5) | 0.001 |
| T score | -3.1 | -2.5 | | -2.9 | -1.8 | |

Values are mean (SD) for continuous variables, and T scores where available. BMD, bone mineral density; BUA, broadband ultrasound attenuation; SOS, speed of sound; VD, vertebral deformity.

however, neither BMD nor QUS variables could discriminate significantly between patients with and without vertebral deformities in the group currently using corticosteroids. Findings were similar if patients with one deformity only were omitted from the analysis.

There are several limitations to our study. The design is cross sectional, so the exact relation between bone variables and the development of vertebral deformities cannot be determined. Second, as discussed in detail in a previous publication,²⁵ the precision data for QUS were less satisfactory than in some, but not all, other studies.^{16 19 35} T and Z scores were not available for BUA and SOS separately, but for the computed SI only, and different reference populations were used for the two devices. The latter will be the case in most clinical settings, and thus provides information on the practical application of the different bone measurement methods.

Vertebral deformities can be defined by various strategies, including morphometric and visual inspection of the vertebrae. We scored all x rays both morphometrically and semiquantitatively. For the results presented in this paper we used a stringent morphometric definition of deformity.²⁹ All the analyses were repeated applying criteria for vertebral deformities semiquantitatively,³⁰ and the results were largely the same. Deformed vertebrae in the analysed region can artificially increase spine BMD. In this study, we chose

not to exclude fractured vertebrae, as this is rarely done in a clinical setting. However, we reanalysed the data excluding subject with deformed vertebrae measured morphometrically at L2-L4 (12 patients and eight controls). The odds ratio (95% CI) per 1 SD reduction in BMD at the lumbar spine was then 1.37 (1.05 to 1.80) for patients and 1.36 (1.01 to 1.84) for controls. The AUCs were 0.60 (0.50 to 0.71) and 0.65 (0.52 to 0.77), respectively. Thus the results were similar to those given in tables 4, 5A, and 5B.

Conclusions

We found that QUS measurements had comparable ability to DXA to discriminate between rheumatoid patients with and without vertebral deformities on a group basis. Among patients who were currently using corticosteroids, however, neither DXA nor QUS variables could discriminate between patients with and without vertebral deformities. We conclude that QUS can be used as an alternative tool to identify subjects with vertebral deformities in rheumatoid arthritis as well as in postmenopausal osteoporosis. QUS is, however, unlikely to give any clinically relevant additional information to that obtained from DXA. Our findings also suggest that the relations between bone measurements and vertebral deformities are less reliable in current corticosteroid users. Additional longitudinal studies are needed to further explore QUS and DXA as clinical tools for predicting fractures in patients with rheumatoid arthritis.

ACKNOWLEDGEMENTS

This study was supported in part by grants from The Research Council of Norway, Lions Clubs International MD 104 Norway, The Norwegian Rheumatism Association, The Norwegian Women Public Health Association, and The Norwegian Osteoporosis Foundation. None of the sponsors took any part in the design of the study, analysis of results, or writing of the article.

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Table 7 Area under the curve for bone measurements for patients with rheumatoid arthritis with and without current corticosteroid use

| | AUC | SE | 95% CI |
|--|------|------|--------------|
| <i>(A) Current corticosteroid users (n = 98)</i> | | | |
| BMD femoral neck (g/cm ²) | 0.61 | 0.07 | 0.48 to 0.74 |
| BMD total hip (g/cm ²) | 0.60 | 0.07 | 0.46 to 0.74 |
| BMD L2-L4 (g/cm ²) | 0.53 | 0.07 | 0.38 to 0.68 |
| SOS (m/s) | 0.63 | 0.08 | 0.50 to 0.76 |
| BUA (dB/MHz) | 0.62 | 0.07 | 0.49 to 0.75 |
| Stiffness index | 0.63 | 0.07 | 0.50 to 0.76 |
| <i>(B) Not using corticosteroids (n = 112)</i> | | | |
| BMD femoral neck (g/cm ²) | 0.65 | 0.07 | 0.52 to 0.77 |
| BMD total hip (g/cm ²) | 0.68 | 0.06 | 0.55 to 0.80 |
| BMD L2-L4 (g/cm ²) | 0.63 | 0.07 | 0.49 to 0.77 |
| SOS (m/s) | 0.70 | 0.07 | 0.56 to 0.82 |
| BUA (dB/MHz) | 0.71 | 0.06 | 0.59 to 0.83 |
| Stiffness index | 0.72 | 0.06 | 0.59 to 0.84 |

AUC, area under the curve; BMD, bone mineral density; BUA, broadband ultrasound attenuation; CI, confidence interval; OR, odds ratio; SE, standard error; SOS, speed of sound.

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