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Original Article

Efficiency of Quantitative Ultrasound Measurements as Compared with Dual-Energy X-ray Absorptiometry in the Assessment of Corticosteroid-Induced Bone Impairment

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Abstract. Bone loss due to corticosteroid treatment differs from that of postmenopausal osteoporosis with regard to bone structure. Corticosteroids affect both horizontal and vertical trabeculae while horizontal trabeculae are damaged in postmenopausal osteoporosis. Dual-energy X-ray absorptiometry (DXA) is the gold standard to evaluate bone loss. The place of quantitative ultrasound (QUS), a technique that could theoretically provide information on bone structure, is not well established in corticosteroid-induced bone impairment. The aim of the study was to determine the usefulness of QUS in the assessment of corticosteroid-induced bone impairment. We hypothesized that the relationship between QUS and DXA could be influenced by changes in bone structure and thus differ with regard to corticosteroid treatment. Seventy-seven women with inflammatory diseases chronically treated with corticosteroids (dose: 7.5–15 mg/day), 29 without corticosteroids and 100 controls were investigated. Bone mineral density at the lumbar spine (BMDL) was measured by DXA and QUS parameters were measured at the calcaneus. Both the QUS parameters (SOS, BUA, Stiffness) and BMDL were significantly lower (by 1.3% for SOS, 5.8% for BUA, 12.7% for Stiffness and 11% for BMDL) in patients treated with corticosteroids compared with patients not taking corticosteroids and with controls ($p<0.001$, ANCOVA, with age and height as covariates). Multiple linear regressions of Stiffness, SOS and BUA as dependent variables on age, BMDL, corticosteroid treatment and a computed new variable designed to test the interaction between BMDL and the treatment group showed that Stiffness, SOS and BUA were dependent on age and BMDL ($p<0.001$); BUA and Stiffness were dependent on treatment group. Taking into account the age of the patients, a significant difference was observed in the relation between BUA and BMDL according to treatment with corticosteroids. A similar difference was found in the subgroup of patients without fractures. SOS and BUA were strongly correlated but their relation did not differ according to treatment. Thus, QUS is useful in the assessment of corticosteroid-associated bone loss. Furthermore, the observation of a significant difference in the relationship between BUA and BMDL with regard to corticosteroid treatment might support the hypothesis that QUS, especially BUA, could give additional information about bone structure.

Keywords: Bone measurements; Corticosteroids; DXA; Osteoporosis; Ultrasound

Introduction

Several techniques are available to estimate bone mineral density (BMD), which accounts for about 70% of bone strength [1]. Bone fragility depends on bone density and also on bone microarchitecture [2], which is not assessed by conventional bone measurements with dual-energy X-ray absorptiometry (DXA). Several noninvasive techniques such as computed tomography with fractal analysis, magnetic resonance or ultrasound

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are under investigation for this purpose [3]. Ultrasound waves passing through bone could theoretically give some information on bone structure in addition to assessing bone density [4]. Most experimental data support the hypothesis that quantitative ultrasound (QUS) can give information on bone structure and is not just a surrogate for BMD [5,6]. Several clinical studies on osteoporosis could not, however, demonstrate such properties [7,8].

There is radiologic [9] and histomorphometric [10] evidence that corticosteroids affect both vertical and horizontal trabeculae, in contrast to the pattern observed in postmenopausal osteoporosis where the horizontal trabeculae are damaged before the vertical ones. Since it has been shown from ex vivo studies that the propagation of ultrasound waves varies according to the orientation of bone trabeculae with respect to the ultrasound source [11], we hypothesized that the relationship between QUS and DXA could differ in corticosteroid-induced bone impairment as compared with postmenopausal osteoporosis. The present study was undertaken to investigate the usefulness of QUS compared with DXA for detecting bone impairment in patients taking corticosteroids, and to analyze whether the relationship between QUS and DXA differed according to the exposure to corticosteroids.

Materials and Methods

Patients

We investigated 77 women treated chronically with corticosteroids. According to ACR criteria and the Uveitis Study Group recommendations [12–14], these patients had rheumatoid arthritis (n = 38), connective tissue diseases (n = 11), vasculitis (n = 8) and sarcoidosis (n = 9); 11 had miscellaneous inflammatory diseases. They had received oral prednisolone or equivalent at a dose of 7.5–15 mg/day for at least 1 year (median duration of treatment 6.8 years, range 1–18 years). Twenty-nine patients with similar diseases not taking corticosteroids underwent DXA and QUS measurements during the same period. Patients in the control group (n = 100) were selected from our data base (patients referred for bone mass evaluation) and were matched with the patients treated with corticosteroids for age and fracture prevalence. The clinical characteristics of the patients included in the three groups are presented in Table 1. None of the patients had renal, hepatic, neurologic, gastrointestinal or metabolic disorders that could alter bone metabolism. In the previous 12 months patients had not used drugs known to affect bone metabolism such as hormone replacement therapy, androgens, calcitonin, bisphosphonates, fluoride salts, anticonvulsivants or heparin. None of these drugs had been used for more than 6 months. The protocol was approved by the hospital local ethics committee and patients were included after giving their oral informed consent.

Fragility fractures were assessed from the medical records. They were defined as a fracture of a vertebra, rib, wrist or hip occurring spontaneously or after minimal trauma (i.e., a fall from standing height). Vertebral fractures were assessed by visual inspection by a radiologist and a rheumatologist according to the recommendations of Kleerekoper and Nelson [15].

Bone Measurements

Anteroposterior BMD of the lumbar spine (BMDL) was measured by DXA (Hologic, QDR 1000, Waltham, MA) and QUS of the right calcaneus by an Achilles device (Achilles, Lunar, Madison, WI). In the case of unilateral right foot pathology (oedema, algodystrophy, etc.), the left heel was measured. Measurements were performed with the patient's heel positioned in a small temperature-controlled warm water bath (37 °C) to eliminate attenuation of ultrasound by air. The system uses a transmitting transducer, with a central frequency of 0.5 MHz, which is electrically excited to produce a broadband spectrum. The ultrasonic wave is transmitted through the heel, detected by a receiving transducer and digitized for computer analysis. Three parameters were measured: SOS (m/s), the velocity of the ultrasonic wave as it passes through the heel; BUA (dB/MHz), a measurement of the frequency-dependent attenuation of the ultrasonic wave as it passes through the heel, relative to its passage through water; and Stiffness, a combined parameter derived from BUA and SOS and calculated from the equation: [0.67 BUA + 0.28 SOS −420]. This parameter, although called Stiffness, does not reflect the homonymous mechanical property [16].

Table 1. Clinical characteristics of patients with inflammatory diseases treated with corticosteroids or without corticosteroids and controls

Parameters	Patients treated with corticosteroids (n = 77)	Patients treated without corticosteroids (n = 29)	Controls (n = 100)
Fractures, any site (n)	42 (56%)	6 (21%)	47 (47%)
Vertebral fractures (n)	31 (73%)	2 (30%)	31 (31%)
Age (years)	59±12	50±14[a]	58±10
Weight (kg)	62±13	65±11	63±9
Height (cm)	158±7[b]	160±6	162±6

[a] p<0.001 versus patients treated with corticosteroids and controls; [b] p<0.0005 versus controls (ANCOVA, Tukey test).

Statistical Analysis

Results were expressed as means and standard deviations (SD). Comparisons of means among the three groups were performed using one-way analysis of variance followed by a post-hoc Tukey test for clinical characteristics. Since age and height differed between groups, analysis of variance with age and height as covariates was applied for QUS and DXA parameters; in the case of statistical effect simple contrast analysis was used to identify which group differed from the others. To test differences between the behavior of QUS and BMD, we used multiple linear regressions (method enter) of the dependent variables Stiffness, SOS, BUA with age, treatment with corticosteroids, BMDL and a new computed variable (treatment ∗ BMDL). This variable was designed to test the interaction between BMDL and the treatment group. We used as software the Statistical Package for Social Science (SPSS, Chicago, IL).

Results

As shown in Table 1, patients not taking corticosteroids were significantly younger than the corticosteroid-treated patients and control patients, although they were in the same decade (50–60 years). The height of corticosteroid-treated patients was significantly lower than that of the controls. Fractures were present in 42 of 77 (56%) corticosteroid-treated patients, in 6 of 29 (21%) patients not treated with corticosteroids and in 47 of 100 (47%) controls. Among patients with fractures, at least one vertebral fracture was present in 31 of 42 (73%) patients treated with corticosteroids, in 2 of 6 (33%) patients without corticosteroids and in 31 of 47 (31%) controls. Table 2 shows that QUS and DXA measurements were significantly different among the three groups ($p<0.001$, ANCOVA with age and height as covariates). Corticosteroid-treated patients had significantly lower SOS, BUA, Stiffness and BMDL than controls ($p<0.001$). Compared with patients not taking corticosteroids, SOS, Stiffness and BMDL were significantly lower in patients taking corticosteroids ($p<0.001$, $p=0.004$, $p<0.001$, respectively) while BUA was not ($p=0.12$). Relative to the controls, corticosteroid-treated patients showed a decrease of 1.3% in SOS, 5.8% in BUA, 12.7% in Stiffness and 11.0% in BMDL. Patients not taking corticosteroids were not statistically different from controls as regards SOS, BUA, Stiffness and BMDL (p = 0.46, 0.67, 0.73, 0.07, respectively).

Multiple regression analysis performed on the whole set of patients showed that Stiffness was significantly dependent on age ($p<0.001$), BMDL ($p<0.001$) and corticosteroid treatment ($p=0.027$). There was no significant difference in the relation between Stiffness and BMDL according to corticosteroid treatment after adjustment for age (p = 0.08). SOS was significantly dependent on age ($p<0.001$) and BMDL ($p<0.001$). BUA was signficantly dependent on age ($p<0.001$), BMDL ($p<0.001$) and corticosteroid treatment ($p=0.013$). A statistically significant difference was found in the relation between BUA and BMDL according to corticosteroid treatment after adjustment for age ($p=0.025$). The equations of the regression lines were: BUA = 91 — 0.36 age + 42 BMDL for corticosteroid-treated patients and BUA = 111 — 0.36 age + 21 BMDL for all those not treated by corticosteroids including the controls (Fig. 1). The subjects in the three groups were then divided into two subgroups according to the presence of fractures and a similar analysis performed. In the subgroup with fractures there was no significant difference in the relation between Stiffness, SOS, BUA and BMDL according to corticosteroid treatment after adjustment for (p = 0.07, 0.18, 0.27, respectively). In the subgroup without fractures the relation between BUA and BMDL was significantly different according to corticosteroid

Table 2. QUS and DXA parameters in patients with inflammatory diseases treated with corticosteroids or without corticosteroids and controls

Parameters	Patients treated with corticosteroids (n = 77)	Patients treated without corticosteroids (n = 29)	Controls (n = 100)
SOS (m/s	1496.6±31.2[a]	1526.7±28.4	1516.6±33.8
T-score	−1.21±1.18	−0.29±1.17	−0.31±1.21
Delta/controls (%)	−1.3	+0.7	
BUA (dB/MHz)	103.6±12.6[a]	112.2±8.4	110.0±13.2
T-score	−1.02±1.171	−0.48±1.25	−0.46±1.31
Delta/controls (%)	−5.8	+2.0	
Stiffness (U)	67.5±16.1[a]	82.8±12.3	77.3±16.7
T-score	−1.05±1.33	−0.17±1.24	−0.12±1.33
Delta/controls (%)	−12.7	+7.1	
Lumbar BMD (g/cm^2)	0.81±0.15[a]	1.0±0.13	0.91±0.17
T-score	−1.03±1.39	−0.03±1.38	−0.10±1.39
Delta/controls (%)	−11.0	+9.9	

[a] $p<0.01$ patients with inflammatory diseases treated with corticosteroids versus those treated without corticosteroids and controls (ANCOVA with age and height as covariate, simple contrast analysis).

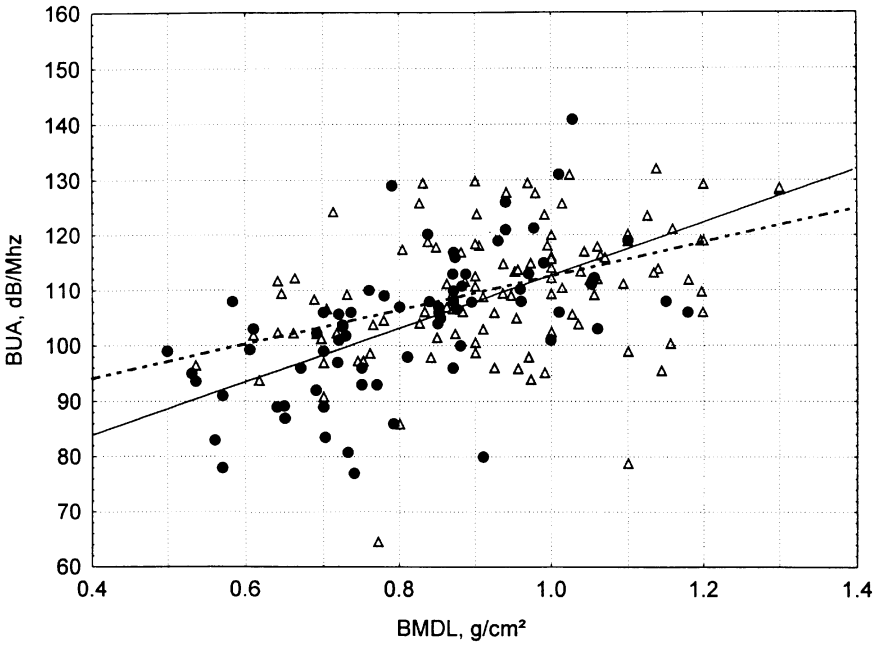

Fig. 1. Regression lines of BUA on BMDL in the three groups (n = 206) according to corticosteroid treatment: *open triangles*, without corticosteroids; *filled circles*, with corticosteroids. The slopes were significantly different (p=0.023).

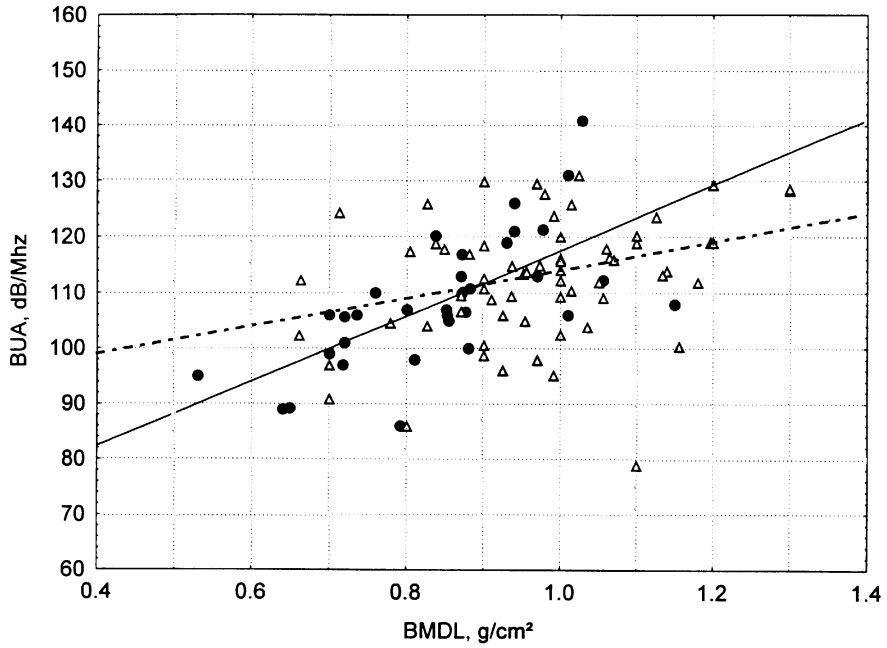

Fig. 2. Regression lines of BUA on BMDL in the subgroup without fractures (n = 96) according to corticosteroid treatment: *open triangles*, without corticosteroids; *filled circles*, with corticosteroids. The slopes were significantly different (p=0.02).

treatment, after adjustment for age ($p = 0.02$). The equations of the regression lines were: BUA = 82.0 — 0.28 age + 51 BMDL for patients on corticosteroids and BUA = 110 — 0.28 age + 19 BMDL for those not on corticosteroids (Fig. 2). A significant relation was observed between SOS and BUA but this did not differ according to corticosteroid treatment.

Discussion

Though the ability of QUS to identify patients with decreased BMD and increased fracture risk has recently been established in postmenopausal osteoporosis, there are still few data on patients receiving corticosteroid treatment. In this study, corticosteroid-treated patients

were shorter and the proportion with vertebral fractures was higher compared with the other two groups, reflecting the sensitivity of vertebral trabecular bone to corticosteroids.

The calcaneus could theoretically be an interesting site to assess the effect of corticosteroids on trabecular bone. Lower QUS and DXA parameters were observed indeed in patients treated with corticosteroids when compared with controls and with patients with an inflammatory disease not treated with corticosteroids. Blanckaert et al. [17], using the same QUS device, reported similar results in a group of patients with rheumatoid arthritis: there was a 16% decrease in Stiffness and an 11% decrease in lumbar BMD. Martin et al. [18] found a more important decrease in BUA (31.6%) and in SOS (6.6%) using a CUBA QUS device. Their results and ours indicate that QUS bone measurements at the calcaneus can detect the effect of low doses of corticosteroids on bone with a sensitivity similar to that of DXA at the lumbar spine. The observed effects are in the range expected when low doses of corticosteroids are used [19].

It has often been reported that patients with inflammatory diseases not treated with corticosteroids have decreased BMD compared with matched controls. There is no consensus, however, and patients with normal BMD have also been reported [19,20]. In the present study, using ANCOVA analysis with age and height as covariates, patients with inflammatory diseases who did not receive corticosteroids differed from corticosteroid-treated patients but not from controls with regard to DXA and QUS parameters.

Multiple regression analysis on the whole set of patients showed that QUS parameters were dependent on age, BMDL and corticosteroid treatment. There is an important structural difference between postmenopausal and corticosteroids-induced bone loss: in the latter there is a general thinning of both horizontal and vertical trabeculae without disappearance of trabeculae; in postmenopausal osteoporosis there is trabecular breakage and horizontal trabeculae are more frequently affected [21,22]. The radiologic evidence for this was reported 15 years ago by Maldague et al. [9]: an ‘empty vertebra’ in corticosteroid-induced osteoporosis and a ‘raining vertebra’ in postmenopausal osteoporosis. Thus we hypothesized that the relation between QUS and DXA would differ according to corticosteroid treatment. Taking into account patient age, we indeed found that the relation between BUA and BMDL differed according to corticosteroid treatment, both for the whole group and for the subgroup of patients without fractures: the relation between BUA and BMDL was stronger in patients receiving corticosteroids. It was closer to that observed in a group of normal subjects (data not shown); this is consistent with the maintenance of normal trabeculation with thinner trabeculae in corticosteroid-induced bone impairment. This difference in the relationship between QUS and DXA according to corticosteroid treatment was found for BUA only. These findings support the hypothesis that BUA might contain some information additional to DXA (BMDL) in the evaluation of bone exposed to corticosteroids. This is in keeping with the properties of BUA, which is determined by bone density and, to some extent, by bone microarchitecture. Experimental studies performed on bovine or human cancellous bone specimens [23] or phantom material [24] have shown that BUA is influenced by structural factors such as pore size and number, though SOS is determined by bone density and elasticity [25]. In addition to the effects on trabecular thickness, the increase in bone marrow fat content caused by corticosteroids could interfere with both QUS and DXA bone measurements and modify the DXA/QUS relation [26]. However, when bone marrow was replaced by water in ex vivo bone specimens, SOS increased and BUA decreased but the correlations between the QUS parameters and BMD assessed by single photon absorptiometry remained unchanged [27].

In conclusion, we have shown that QUS at the calcaneus can be useful in the assessment of corticosteroid-induced bone impairment. In addition, the different relationship between BUA and BMDL with regard to corticosteroid treatment illustrates the contribution of each technique to bone evaluation. The modest contribution of bone ‘quality’ to determining the strength of bone compared with bone density might explain the difficulties encountered in clinical situations when trying to show that QUS is not a simple surrogate of BMD [5,28].

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