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Original Article

Bone mineral density in haemodialysis patients: A comparative study of dual-energy X-ray absorptiometry and quantitative ultrasound

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Abstract

Background. Quantitative ultrasound (QUS) of bone is a relatively new technique that appears to assess 'bone quality' in addition to bone mineral density. The purpose of this study was to evaluate the diagnostic potential of QUS of calcaneum and to correlate it with dual energy X-ray absorptiometry (DEXA) in chronic haemodialysis patients.

Methods. Broad-band ultrasound attenuation (BUA; dB/MHz) and speed of sound (SOS; m/s) of calcaneum and DEXA (g/cm^2) measurements of the lumbar spine and hip were made in 39 patients. The indices obtained by either method were compared with age-and sex-matched controls. Calcaneal measurements were correlated to DEXA and relevant clinical and biochemical data of patients.

Results. BUA and SOS values were markedly reduced in dialysis patients compared to controls (59.1 ± 13.8 *vs* 73.0 ± 16.2 dB/MHz, $P < 0.001$ and 1533 ± 28 *vs* 1560 ± 29 m/s, $P = 0.014$ respectively). There was a moderate, but significant association between calcaneal parameters and DEXA ($r = 0.32$–0.53, $P < 0.05$). Both BUA and SOS scores were inversely correlated with age ($r = -0.69$, $P < 0.001$) and duration of menopause ($r = -0.74$, $P < 0.01$). Additionally, BUA values showed a moderate negative association with serum intact parathyroid values ($r = -0.38$, $P = 0.018$).

Conclusion. Chronic haemodialysis patients have reduced calcaneal BUA and SOS scores. QUS of the calcaneum is an easy-to-apply and radiation-free technique. It could be a useful substitute for assessment of bone density in such patients. However, further studies in large patient groups and comparisons with plasma markers of bone turnover and bone biopsy findings are needed to assess its potential place in the management of renal osteodystrophy.

Keywords: bone mineral density; calcaneal ultrasound; dual-energy X-ray absorptiometry; haemodialysis; quantitative ultrasound

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Introduction

Renal osteodystrophy (ROD) continues to be a cause of significant morbidity and mortality in end-stage renal failure patients [1]. A recent study has demonstrated that fracture risk is generally increased in these patients [2]. As the mechanical strength and the fracture risk of bone are determined by the amount of mineralized matrix, the assessment of bone mineral density (BMD) is of great clinical importance [3]. Among several invasive and non-invasive methods to assess BMD, bone densitometry in particular dual-energy X-ray absorptiometry (DEXA) is the currently preferred and most widely used technique. The studies that measured BMD in dialysis patients by various densitometry methods, however, demonstrated quite variable results [3].

Quantitative ultrasound (QUS) of bone is a relatively new technique that appears to assess bone elasticity and microarchitecture in addition to BMD [4]. The two QUS parameters currently measured are broad-band ultrasound attenuation (BUA) and speed of sound (SOS). SOS is related to elasticity and density of bone whereas BUA is related to bone density and structure. *In-vitro* studies showed that BUA was associated with trabecular orientation, trabecular spacing, and connectivity [5,6].

Several cross-sectional and retrospective studies in healthy adults comparing QUS of calcaneum and BMD measured by DEXA found QUS to be as good as densitometry (reviewed in [4]). Two recent prospective trials have also shown that calcaneal BUA was a strong predictor of osteoporotic fractures and may measure 'properties of bone independent of bone density' [7,8].

QUS measurement of calcaneum has other advantages. Unlike many other methods, it does not use ionizing radiation and it is cheaper, more portable,

and easier to use than conventional densitometry techniques [4].

The aim of this study was to establish the diagnostic potential of QUS of the calcaneum in chronic haemodialysis (HD) patients by comparing it with DEXA measurements of the lumbar spine and hip. We also evaluated the relationship between QUS parameters and several clinical and biochemical features of bone disease in HD patients.

Subjects and methods

The study included 39 chronic HD patients (19 male, 20 female; mean age 42 ± 13 years) who had been on maintenance HD (mean duration 74 ± 45 months). The underlying renal disorders leading to end-stage renal failure were chronic glomerulonephritis (10 patients), chronic pyelonephritis (four patients), amyloidosis (four patients), diabetic nephropathy (three patients), polycystic kidney disease (three patients), hypertensive nephropathy (two patients), obstructive nephropathy (one patient), and unknown cause (12 patients). Patients with previous renal transplantation, parathyroidectomy, or with diseases, conditions, or medications (glucocorticoids, anticonvulsants, and anticoagulants) that might alter bone mineral metabolism were excluded.

All patients were dialysed for 5 h, 3 times weekly, using cuprophane hollow-fibre dialysers. Dialysis fluid was free of aluminium and contained 2.0 mEq/l calcium. All patients were receiving heparin (2500–6500 units) regularly during dialysis session. Serum phosphate values were controlled by diet and phosphate binder treatment. All but two patients were using calcium carbonate at a mean dose of 4.4 ± 0.3 g/day at the time of the study. Twelve patients (30.7%) were using oral alfacalcidol at doses of 0.32 ± 0.03 μg/day. The calcium, phosphate, alkaline phosphatase, and intact parathyroid hormone (iPTH) levels were measured using standard techniques. Dialysis adequacy was evaluated by urea reduction ratio. Body mass index (BMI) was calculated as the ratio of weight to $(\text{height})^2$ $(\text{kg}/[\text{m}]^2)$.

The control population consisted of healthy adults with no known metabolic bone disease who were age- and sex-matched with the HD patients. The study was carried out in accordance with the Declaration of Helsinki (1989) and informed consent was obtained from all patients.

BMD (g/cm^2) of the lumbar spine (L_1–L_4) and hip (femoral neck, trochanteric, intertrochanteric and Ward triangle) were measured by DEXA (Hologic QDR-1000, Waltham, MA, USA). QUS measurements of calcaneum (Hologic Sahara Sonometry) were done from the non-dependent heel. BUA (dB/MHz) and SOS (m/s) were measured according to the scanning protocol provided by the manufacturer. The QUS measurements were made by one co-author (HE) blind to DEXA results. Reproducibility of QUS was determined in 15 healthy subjects and 10 dialysis patients, each of whom had two separate measurements. The mean coefficient of variations for BUA and SOS were not significantly different between healthy group and HD patients.

The data were presented as mean $\pm$ SD. One-sample t test was applied to test whether the DEXA and QUS measures of the HD population deviate from that of age- and sex-matched control populations. The subgroup analysis for sex and duration of menopause in HD patients were done by two-sample t test. Pearson's correlation coefficient (r) was calculated and tested for significance of linear relationship among variables. A P value <0.05 was considered to be significant. All data were analysed using SPSS v 6.0 for Windows (SPSS Inc.).

Results

The demographic and biochemical parameters of patients are shown in Table 1. Ten of the females (50%) in HD group were post-menopausal; none of them had received hormone replacement therapy. Among age- and sex-matched control group, nine of 20 females (45%) were in menopause with a similar duration (120 ± 82 months *vs* 114 ± 98 months, $P = 0.88$). BMI of control population was higher than patient group (24.9 ± 2.3 kg/m^2 *vs* 22.7 ± 3.8 kg/m^2) but the difference was not significant.

The correlation of QUS parameters of calcaneum with BMD measured at the lumbar spine and hip by DEXA is shown in Table 2. BUA was significantly associated with BMD at the spine and hip in both HD patients and controls. There was also a correlation between all BMD measures and SOS in controls, but SOS values failed to correlate with spine, intertrochanteric and Ward triangle BMD of HD patients.

In the 39 patients who had been on dialysis, the BMD measurements at the hip and QUS parameters of calcaneum were significantly lower than controls. The QUS parameters of calcaneum were lower in female patients (BUA, 60.5 ± 14.1 dB/MHz; SOS, 1537 ± 25 m/s) compared to males (BUA, 62.8 ± 14.7 dB/MHz; SOS, 1547.57 ± 26.52 m/s) but the difference was not significant. These parameters were further reduced in post-menopausal females (BUA, 52.71 ± 10.50 dB/MHz; SOS, 1511.02 ± 23.24 m/s) and were significantly different from male dialysis patient values ($P > 0.05$). There was no difference between spine BMD values of HD patients and the control population (Table 3).

The BUA and SOS measurements were significantly correlated both in HD group and controls (HD: $r = 0.57$, $P < 0.001$ and control: $r = 0.60$, $P < 0.001$).

The calcaneal BUA values were inversely correlated with age of patients and duration of menopause (Table 4). Among the clinical and biochemical parameters of HD patients, serum iPTH values were inversely correlated with BUA of calcaneum (Table 4 Figure 1). The degree of association with BUA and iPTH was more significant in post-menopausal females ($r = -0.78$, $P = 0.008$). The SOS scores of patients were only correlated with age and duration of menopause. No association between QUS parameters and duration of dialysis was detected (Table 4).

Discussion

The increased susceptibility to fracture is the most important clinical manifestation of all metabolic bone diseases, including renal osteodystrophy [3]. Dialysis patients are likely to have low BMD due to a combination of several alterations in mineral and bone

Table 1. Clinical and biochemical data of haemodialysis patients ($n=39$)

	Mean ± SD (range)	Reference range
Age (years)	42 ± 13 (18–70)	NA
Males ($n=19$)	39 ± 12 (18–64)	
Females ($n=20$)	45 ± 13 (22–70)	
Post menopausal females ($n=10$)	53 ± 11 (31–70)	
Duration of menopause (months)	114 ± 98 (12–336)	
Body mass index (kg/m^2)	22.7 ± 3.7 (17.7–34.4)	NA
Duration of HD (months)	74 ± 45 (6–160)	NA
Serum calcium (mg/dl)	9.3 ± 0.8 (7.4–11.4)	8.5–10.4
Serum phosphate (mg/dl)	5.1 ± 1.8 (1.2–9.2)	2.5–4.5
Serum alkaline phosphatase (IU/l)	317 ± 220 (82–976)	40–130
Serum intact PTH (pg/ml)	195 ± 250 (12–1233)	10–60
Urea reduction ratio (%)	67.3 ± 4.6 (63.4–68.2)	>65

HD, haemodialysis; PTH, parathyroid hormone.

Table 2. Correlation coefficients of calcanea QUS parameters with BMD at spine, femoral neck, trochanteric, intertrochanteric (IT) and Ward triangle sites of hip in HD patients and controls

BMD	Haemodialysis patients				Controls			
	BUA		SOS		BUA		SOS	
	r	*P*	*r*	*P*	*r*	*P*	*r*	*P*
Spine	0.32	0.047	0.26	NA	0.54	<0.001	0.43	0.005
FN	0.39	0.013	0.36	0.025	0.45	0.004	0.44	0.005
IT	0.43	0.006	0.38	0.018	0.47	0.006	0.40	0.020
T	0.53	<0.001	0.42	0.008	0.58	<0.001	0.44	0.005
WT	0.32	0.048	0.22	NS	0.58	<0.001	0.36	0.022

BUA, broad-band ultrasound attenuation; SOS, speed of sound; *r*, correlation coefficients; FN, femoral neck; IT, intertrochanteric; T, trochanteric; WT, Ward triangle.

Table 3. Bone mineral density data of HD patients and controls

	Haemodialysis	Control	*P*
Spine (g/cm^2)	0.926 ± 0.15	0.935 ± 0.15	0.76
Femur neck (g/cm^2)	0.678 ± 0.13	0.795 ± 0.12	<0.001
Intertrochanteric (g/cm^2)	0.847 ± 0.14	1.057 ± 0.16	<0.001
Trochanteric (g/cm^2)	0.552 ± 0.10	0.686 ± 0.12	<0.001
Ward triangle (g/cm^2)	0.587 ± 0.19	0.707 ± 0.19	<0.001
BUA (dB/MHz)	58.09 ± 13.75	73.04 ± 16.19	<0.001
SOS (m/s)	1533.3 ± 28.1	1559.5 ± 28.8	0.014

Table 4. Correlation coefficients of calcaneal QUS parameters with clinical and biochemical parameters of HD patients

	n	BUA		SOS	
		r	*P*	*r*	*P*
Age	39	−0.69	<0.001	−0.48	0.002
Duration of menopause	10	−0.74	<0.01	−0.61	0.048
Duration of dialysis	39	−0.21	NS	−0.04	NS
Body mass index	39	−0.24	NS	−0.13	NS
Serum iPTH	39	−0.38	0.018	−0.02	NS

metabolism. The presence of numerous confounding factors not only cause major alterations in bone structure but make ROD the most complex and least predictive form of metabolic bone disease [3].

The major findings of this study were the reduced calcaneal QUS parameters, namely BUA and SOS, in chronic HD patients compared with age- and sex-matched normal controls, and moderate but significant

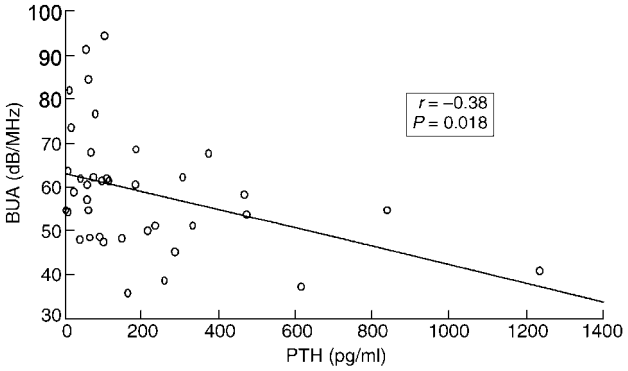

Fig. 1. The inverse correlation of calcaneal broad-band ultrasound measures and serum intact parathyroid hormone levels in haemodialysis patients.

correlation between QUS of calcaneum and DEXA of HD patients.

QUS of bone is a promising, relatively new technique that assesses BMD non-invasively without using ionizing radiation. A large number of cross-sectional and prospective studies in normal, healthy populations have demonstrated that QUS has a diagnostic potential similar to DEXA [4], and an even more predictive power for fracture risk [8]. There is, however, less information about the role of this novel technology in patients with renal failure [9,10]. Rico *et al.* were first to use ultrasound bone velocity and found that both ultrasound bone velocity and metacarpal radiogrammetry were significantly lower in haemodialysis patients [9]. Later, Foldes *et al.* showed that SOS measurements were substantially reduced in dialysis patients. They also demonstrated an association between SOS values and time on dialysis and serum parathyroid hormone (PTH) values [10].

In this study we performed QUS of calcaneum, which was the most widely used bone for ultrasonic measurements, and correlated the results with DEXA values from the lumbar spine and hip. We observed a significant reduction in BUA (59.1 ± 13.8 *vs* 73.0 ± 16.2 dB/MHz, $P < 0.001$) and SOS (1533 ± 28 *vs* 1560 ± 29 m/s, $P = 0.014$) values compared to controls. The absence of an established national database for QUS of calcaneum precluded us from calculating Z and T scores for the HD population. Nevertheless a highly significant difference implies that calcaneal QUS may be useful in detecting low BMD in chronic HD patients. Moreover, the observed difference in QUS parameters was consistent with DEXA values obtained from the hip. We failed to detect a significant difference for the lumbar spine DEXA among patients and controls, in accordance with previous reports [11,12].

The QUS parameters of chronic HD patients had an inverse relationship to age. Age-related changes in QUS scores are well defined in the general population [4]. QUS parameters were lower in females than in males, and were significantly different in post-menopausal females. This finding was compatible with previously reported studies indicating a 'preferential bone mineral loss in post-menopausal dialysed women' [13,14]. We failed to observe any association between calcaneal parameters and duration of dialysis. This observation is in agreement with some previous reports [11,15], but a recent study that evaluated nearly 500 000 dialysis patients demonstrated a great increase in the risk of hip fracture related to an increased duration of dialysis [16]. The lack of correlation in this study may be related to the structural characteristics of the calcaneal bone, which is almost exclusively trabecular. Although reduction in trabecular bone density has been shown in dialysis patients [17], the major alteration in bone structure was generalised cortical thinning [3]. Moreover, Foldes *et al.*, using a highly cortical bone, detected an association between tibial SOS values and duration of dialysis [10].

There was a moderate, but significant negative association between BUA measurements and serum iPTH levels ($r = -0.38$, $P = 0.018$) of HD patients. The degree of association was greater in post-menopausal females ($r = -0.78$, $P = 0.008$), which indicates the role of oestrogen in opposing the PTH effect on bone [14]. *In vitro* studies by Glüer *et al.* have confirmed that BUA values correlate with histomorphometric parameters of trabecular structure and alignment in normal bone [5,6]. As abnormally elevated PTH values are known to create marked irregularities in the bone microarchitecture of uraemic patients, the relevance of the association between BUA and PTH should be explored further in larger groups of patients and correlated with bone histomorphometry. The absence of correlation between SOS values and iPTH contradicted a previous report [10] and again this may be related to the trabecular character of calcaneum.

These data from a selected, small group of chronic HD patients have also shown a significant correlation between calcaneal QUS parameters and DEXA measures. The best correlations were observed between BUA values and intertrochanteric, trochanteric and femoral neck DEXA ($r = 0.39$–0.53). SOS values were also correlated with these sites, but correlation coefficients were lower ($r = 0.36$–0.42). The BUA correlations with lumbar spine and Ward triangle were not as good ($r = 0.32$); SOS values were not correlated at all. The poor correlations with the lumbar spine (spurious effects of osteophytes, aortic calcifications) or Ward triangle (a predominantly cortical site) may be related to either differential involvement of ROD in different skeletal sites [18] or the ability of bone QUS to measure 'bone quality' beyond BMD [4,8]. Comparative studies involving larger groups of HD patients and the general population are necessary to determine the cause.

In summary, this study showed that QUS parameters from calcaneum were markedly reduced in chronic HD patients compared with parameters of an age- and sex-matched healthy population. QUS is a simple and radiation-free technique and it may be useful in detecting reduced bone density in dialysis patients. However, further studies in larger patient groups, including predialysis patients, and comparisons with

non-invasive (plasma bone turnover markers, quantitative computed tomography) and invasive (bone histomorphometry) markers of ROD are needed to define the full clinical value of QUS.

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