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Original Article

Quantitative Ultrasound of Phalanges and Dual-Energy X-ray Absorptiometry of Forearm and Hand in Patients with End-Stage Renal Failure Treated with Dialysis

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Abstract. The aim of the study was to evaluate the usefulness of quantitative ultrasound (QUS) measurement of the proximal phalanges of the hand in patients with end-stage renal failure (ESRF) treated with dialysis, and to compare results of this method with those from dual-energy X-ray absorptiometry (DXA) of hands and forearms (shaft and ultradistal site). Forty-one men aged 48.1 ± 11.7 years and 31 women aged 43.1 ± 12.3 years were examined. Mean QUS values of the hands in men and women with ESRF were significantly lower than the values of the healthy control group. There was a significant positive correlation between QUS and DXA of fingers, hands and also forearms, more pronounced in the shaft than in the ultradistal site. There was no significant difference in the measurements of extremities with or without a fistula. We conclude that QUS measurements are decreased in patients with ESRF treated with dialysis, and they correlate with DXA results. The simplicity of QUS makes it a valuable method in everyday practice. The clinical significance of the QUS results in these patients with ESRF treated with dialysis needs further investigation.

Keywords: Chronic renal failure; Dialysis; Dual-energy X-ray absorptiometry; Quantitative ultrasound; Renal osteodystrophy

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Introduction

Renal osteodystrophy is one of the most important complications of chronic renal failure (CRF), and bone loss is frequently seen already in the early phase of CRF [1]. Renal osteodystrophy as a metabolic disease is characterized by major changes in bone turnover. The rate of formation or degradation of bone matrix can be assessed by measuring the activity of specific biochemical markers of bone metabolism [1]. There are a number of methods for evaluation of bone mineral density (BMD) but dual-energy X-ray absorptiometry (DXA) is the most widely used. This method is considered to be valuable for predicting the risk of bone fracture in osteoporosis, but its usefulness in CRF is not clear. There are patients with osteoporosis and bone fragility higher than one could expect only from the degree of bone demineralization [2], so predisposition to bone fractures must depend not only on bone osteopenia measured by DXA but also on other changes in bone structure.

From mechanical principles it is obvious that the strength of an object does not depend only on the quantity of material from which it is constructed but also on its internal structure, its shape, and the physical properties of its constituents [3]. Quantitative ultrasound (QUS) measurement of bone is a method that seems to provide important information about bone quality. Certain authors claim that ultrasonic measurements appear to reflect mainly bone quantity [4,5]; however, others have found that QUS parameters are associated with bone structure [3,6].

Besides its use in postmenopausal osteoporosis [7], QUS of the phalanges has been performed in epileptic patients after long-term anticonvulsant therapy [8] and in hemodialyzed patients [9]. The proximal phalanges were chosen as the measurement site because they are composed of both cortical and cancellous bone [10]. Human phalanges are one of the sites where the first changes in bone tissue can be recognized [11]; therefore they were the main site we were interested in for measuring bone changes in our group of patients.

The aim of the study was to evaluate the correlation between the results of QUS and of DXA, together with some biochemical and clinical data in patients with renal osteodystrophy treated with dialysis, and to evaluate the usefulness of QUS when compared with DXA in the diagnosis of bone changes in these patients.

Patients and Methods

Seventy-two patients with end-stage renal failure (ESRF) were examined. There were 41 men aged 48.1 ± 11.7 years (range 21–70 years) and 31 women aged 43.1 ± 12.3 years (range 18–66 years). The reason for CRF was chronic glomerulonephritis in 51 patients, chronic pyelonephritis in 10, diabetic nephropathy in 5, polycystic kidney disease in 4 and other reasons in 2. Sixty-four patients were treated with hemodialysis (HD) and 8 with continuous ambulatory peritoneal dialysis (CAPD). Two of the HD patients had been treated previously with CAPD and 1 CAPD patient had been treated previously with HD. The patients with HD were dialyzed for 3–4 h 3 times a week with a calcium concentration in the dialysis fluid of 1.25 mmol/l. Forty-two patients had a fistula on the left forearm and 21 had a fistula on the right forearm; one patient had a fistula on the leg. The patients with CAPD had 4 changes a day of peritoneal fluid with a calcium concentration of 1.25 mmol/l. Nine women were premenopausal; 3 of them received hormone replacement therapy. All patients received calcium carbonate 1.0 g three times a day and 23 of them had received 1α-hydroxycholecalciferol (Alphacalcidolum, Polfa) at a dose of 0.25 μg/day for at least the previous 6 months.

The control group consisted of 90 women aged 45.8 ± 10.6 years and 20 men aged 52.2 ± 12.8 years recruited from attenders of Outpatient Osteoporotic Clinic. The patients from the control group had only QUS examinations. The age, weight and height of the controls did not differ significantly from those of the study group. The clinical characteristics of the patients and controls are presented in Table 1.

QUS was performed with a DBM Sonic 1200 (Igea, Italy) device. The system calculates the amplitude-dependent speed of sound (Ad-SOS) automatically. The SOS value is influenced by phalanx thickness and the time required to cross the phalanx. Ad-SOS was measured in the soft tissue of the first interdigital space to take account of soft tissue interference. The measurements were performed at the distal metaphysis of the proximal phalanges of four fingers of both hands (II–V finger). The final result was expressed as the mean value of these four measurements, in meters per second.

BMD examinations were performed with DXA using a Lunar DPX-L (Lunar, Madison, WI). BMD was measured in both forearms at the ultradistal and shaft sites of the radius and also in both hands. BMD of the hands was evaluated manually using the program for the total body of small animals. Separately (using the same program for small animals), BMD was evaluated in every distal metaphysis in the proximal phalanges of four fingers of both hands (II–V finger), at the same location where the QUS examination was performed. The mean value of these four measurements was calculated. The method of this examination is presented in Fig. 1. The results of all BMD measurements are expressed in grams per square centimeter and, for the radial bone measurements, in *Z*-score values also. There are no norms established for BMD of hand and fingers.

The following additional tests were performed: serum intact parathyroid hormone (i-PTH), phosphorus and ionized calcium concentrations, alkaline phosphatase (AP) activity, and the activity of the bone fraction of alkaline phosphatase. All blood samples were taken just before HD, or in the morning in the patients treated with CAPD.

The following methods were used for statistical analysis: paired *t*-test, simple linear regression analysis and, if necessary, the Spearman rank correlation test. All values were expressed as the mean ± SD. Results were taken as statistically significant when $p<0.05$.

Table 1. Clinical data

	Control group		Dialyzed patients				
	Body weight (kg)	Height (cm)	Body weight (kg)	Height (cm)	Years since menopause (years)	Duration of CRF (years)	Duration of dialysis (years)
Male	72.9±9.3	172.9±5.2	69.4±10.9	173.4±6.8		10.3±7.3	5.7±5.0
Female	60.5±6.5	161.8±5.3	57.2±12.8	159.6±6.0	8.2±7.7	9.5±6.2	4.9±4.0

CRF, chronic renal failure.
Years since menopause: mean value concerns 22 women.

Manual Analysis*

DEXA Calibration

#	CENTER x,y	Number Of Vertices	BMC g	AREA cm²	BMD g/cm²
1	51, 39	6	24.597	55.735	0.441
2	37, 26	4	0.366	0.892	0.411
3	54, 25	4	0.428	0.979	0.437
4	71, 30	4	0.280	0.749	0.374
5	85, 36	4	0.194	0.634	0.306

+Data altered by exclusion ROI
*Data for research only

Fig. 1. Examination of the hand and fingers with DXA. 1, whole hand; 2, II finger; 3, III finger; 4, IV finger; 5, V finger.

Results

Short-term in vivo reproducibility of QUS was assessed on the basis of 75 measurements in 15 healthy students aged 22–25 years (8 men, 7 women; 5 measurements in each person). The coefficient of variation (CV) was 0.64% and, when expressed as the standardized CV (sCV = CV/(4 SD/mean), where SD and mean are the standard deviation and mean value of subjects included in the reproducibility study), was 7.13%. All measurements were done by the same operator. The reproducibility of the DXA measurement of hand and fingers was calculated on the basis of 10 analyses in each of 5 examinations of the left hand in 5 healthy persons (4 men, 1 woman) aged 24–43 years. All measurements were performed by the same operator. The CV of the whole hand was 0.68%, of the II finger 3.63%, III finger 2.71%, IV finger 3.62% and V finger 4.01%. Standardized CV (expressed as above) of the whole hand was 1.25%, of the II finger 4.08%, III finger 3.75%, IV finger 4.25% and V finger 13.86%.

Biochemical results are shown in Table 2. The results of QUS and DXA measurements of hands, fingers and forearms at the ultradistal and shaft sites in dialyzed patients are presented in Table 3. The results of QUS of the dialyzed men and women compared with the healthy control group are shown in Fig. 2. The comparison of the results of examination of the upper extremity with and without a fistula in 63 patients (42 left, 21 right extremity) is given in Table 4. There were no statistically significant differences between measurements of the two extremities, so the result from the left upper extremity was taken for further investigations. The left side was chosen because of the more comfortable position for the patient during DXA examination of hand. The correlation between the results of QUS and DXA measurements is shown in Table 5.

When we compared results of QUS (m/s) and DXA (g/cm^2) with clinical and biochemical data there was a significant correlation between the duration of CRF and: QUS results in women ($r = -0.4942$, $p = 0.0047$), DXA results of the hand in men ($r = -0.4237$, $p = 0.0058$) and women ($r = -0.5614$, p=0.0012), DXA results of the ultradistal radius in men ($r = -0.4479$, $p = 0.0037$), and DXA results of the radial shaft in men ($r = -0.3960$,

Table 2. Biochemical data in dialyzed patients

	i-PTH (pg/ml)	Ionized Ca (mmol/l)	Phosphorus (mmol/l)	AP (U/l)	Bone fraction of AP (U/l)
Male	309±319	1.54±1.13	2.13±0.49	162±118	80.3±58.0
Female	491±593	1.63±1.21	1.88±0.55	258±271	165 ±196
Normal range	9–55	1.05–1.3	0.64–1.60	42–120	24–34% AP

AP, alkaline phosphatase; i-PTH, intact parathyroid hormone.

Table 3. Results of QUS and DXA measurements in dialyzed patients

	QUS (m/s)		DXA (g/cm^2)							
	Left	Right	Fingers[a]		Hand		Ultradistal radius		Radial shaft	
			Left	Right	Left	Right	Left	Right	Left	Right
Male	1948±96	1946±103	0.386±0.062	0.408±0.061	0.429±0.058	0.441±0.054	0.357±0.085	0.358±0.080	0.710±0.124	0.709±0.11
Female	1915±106	1917±109	0.312±0.049	0.312±0.056	0.357±0.037	0.367±0.038	0.275±0.050	0.295±0.091	0.549±0.112	0.558±0.11

No differences between the results of examinations of the left and right extremity are statistically significant.
[a]Mean value of BMD of the distal metaphysis of the proximal phalanges of four (II–V) fingers.

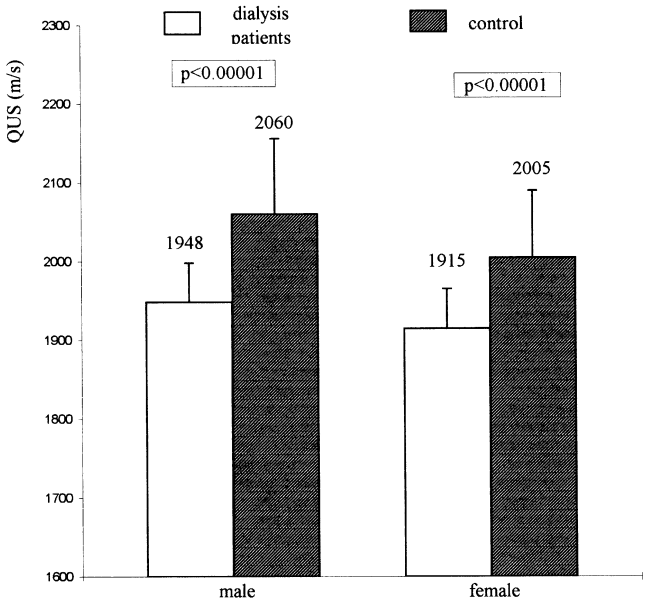

Fig. 2. QUS results of the dialysis patients and the healthy control group (male and female).

Table 4. Comparison between results of examination of the extremity with and without a fistula in 63 patients

	With fistula	Without fistula	Significance
QUS (m/s)	1919±105	1922±100	NS
DXA (g/cm^2)			
Hand	0.404±0.062	0.398±0.062	NS
Ultradistal radius	0.319±0.083	0.329±0.094	NS
Radial shaft	0.634±0.144	0.638±0.144	NS

The fistula was in the left forearm in 42 patients and in the right forearm in 21.

Table 5. Correlation between QUS and DXA results

	DXA (g/cm^2)			
	Fingers[a]	Hand	Ultradistal radius (left)	Radial shaft (left)
QUS (m/s)	0.6756	0.5796	0.4568	0.6682
DXA (g/cm^2)				
Fingers[a]		0.9309	0.7869	0.8895
Hand			0.8734	0.8931
Ultradistal radius (left)				0.7403

[a]Mean value of BMD of the distal metaphyses of the proximal phalanges of four (II–V) fingers.
$p<0.0001$ for all values.

$p = 0.0114$) and women ($r = -0.6309$, $p = 0.0001$). There was a significant correlation between the duration of dialysis treatment and: the QUS results in women ($r = -0.4109$, $p = 0.0216$), the DXA results of the hand in men ($r = -0.3455$, $p = 0.0269$) and women ($r = -0.3978$, $p = 0.0267$), the DXA results of the ultradistal radius in men ($r = -0.3860$, $p = 0.0139$), and the DXA results of the radial shaft in men ($r = -0.5348$, $p = 0.0019$). The immunoreactive PTH serum level was significantly correlated with: the QUS results in men ($r = -0.5388$, $p = 0.0012$), the DXA results of the hand in men ($r = -0.3797$, p=0.0227) and the DXA results of the radial shaft in men ($r = -0.4868$, $p = 0.0035$). There was a statistically significant correlation of serum ionized calcium levels only with the QUS results in men ($r = 0.3317$, $p = 0.0341$). The values of serum phosphorus correlated significantly only with the DXA results of the ultradistal radius in men ($r = 0.3194$, $p = 0.0446$). Serum alkaline phosphatase activity correlated significantly with: the QUS results in men ($r = -0.3464$, $p = 0.0377$) and women ($r = -0.6303$, $p = 0.0013$), the DXA results of the hand in men ($r = -0.4601$, $p = 0.0058$) and women ($r = -0.6461$, $p = 0.0010$), the DXA results of the ultradistal radius in men ($r = -0.3950$, $p = 0.0178$), and the DXA results of the radial shaft in men ($r = -0.5191$, $p = 0.0018$) and women ($r = -0.6963$, $p = 0.005$). Serum activity of the bone fraction of alkaline phosphatase correlated significantly with: the QUS results in women ($r = -0.5893$, $p = 0.0027$), the DXA results of the hand in men ($r = -0.4103$, $p = 0.0138$) and women ($r = -0.5953$, $p = 0.0024$), the DXA results of the ultradistal radius in men ($r = -0.3482$, $p = 0.0367$), and the DXA results of the radial shaft in men ($r = -0.5200$, $p = 0.0018$) and women ($r = -0.6204$, $p = 0.0019$). There was no statistically significant difference between the correlation of AP and AP bone fraction serum activity with the QUS and DXA results.

The correlation coefficient of the simple linear regression concerning the measurements on individual finger with QUS and DXA in both hands ranged between $r = 0.555$, $p<0.0001$ (for II left finger) and $r = 0.657$, $p<0.0001$ (for III right finger).

Discussion

Renal osteodystrophy is a complex disease and often only bone biopsy can distinguish its form, so we were not able to identify the type of renal osteodystrophy on the basis of the QUS results without bone histomorphometry. Although bone demineralization is often seen in CRF, the role of bone densitometry in therapeutic procedures in ESRF has not been assessed, and it seems as though the method does not discriminate the form of renal osteodystrophy. There was no difference in DXA results between the patients with high-turnover and low-turnover bone disease. Conversely, quantitative computed tomography has shown that patients with low-turnover lesions often have a greater reduction in vertebral bone mass than patients with high-turnover bone disease [12]. Another study has shown that the bone mineral content evaluated by bone densitometry is low in most patients, and more associated with bone morphologic signs of osteomalacia than with secondary hyperparathyroidism [13]. Different conclusions may

depend on different measurement sites, with a predominance of cortical or trabecular bone respectively.

We found in present study that the mean value of the QUS results in the group of dialyzed patients was significantly lower than in the healthy control group of men and women comparable in age, weight and height. The same was observed in a previous study concerning QUS measurements in dialyzed patients [9]; this study found a significant correlation between QUS results and metacarpal radiogrammetry. Our present study shows a positive significant correlation between QUS and DXA results in the hand. This was seen when we examined exactly the same region and compared it with BMD of the whole hand. There was positive significant correlation between QUS and DXA of the ultradistal and especially the shaft site of the radius also. This better correlation at the shaft site may depend on the similar structure of the phalangeal metaphysis and the radial shaft, which both have a predominance of cortical bone. Densitometry of the ultradistal radius and radial shaft were better correlated with DXA results of the hand than with QUS of the phalanges. This was probably because the two methods do not measure the same parameter of bone status. QUS has the potential to give more information on bone: not only on the mineralization (as does DXA) but also on bone structure and elasticity [3,14], which is also strongly correlated with BMD. It was postulated in certain studies concerning osteoporosis that a decrease in QUS values is a sign of lower than normal bone elasticity [10], so it is possible that in our patients also a decrease in this bone parameter could exist.

Previous studies have shown that Ad-SOS is stable in premenopausal women (age 45–50 years) [15]. There was a decrease of 0.23% a year in Ad-SOS between the 41–50 and 71–80 year age groups. However, in another study Ad-SOS decreased in a large group of premenopausal women (n = 460) [7]. In our study the results of QUS and all the DXA measurements were weakly correlated with age, body weight and height and also with time of the menopause in women. This may be caused partly by the influence on bone status of metabolic disorders in ESRF, in addition to the typical factors that are important in osteoporosis. When interpreting our results the technical problems regarding accurate orientation of the ultrasound beam with respect to bone structure under in vivo experimental conditions need to be borne in mind, as these can also affect the end results. Duration of CRF had a more pronounced effect on the QUS and DXA results than duration of treatment. In accordance with observations from a previous study using DXA measurements, bone demineralization was found to be induced mainly in the predialysis phase of CRF, and treatment with dialysis could stop these changes [16]. There were no statistically significant differences between the results of QUS and DXA in the two upper extremities and the presence of an arteriovenous fistula was also found to have no influence on the QUS and DXA results, so the examination could be done at the optional site. We decided to examine the left extremity because it allowed a more convenient DXA measurement position for the patient.

There was moderate but significant correlation between DXA and QUS examinations and serum i-PTH only in men. This may suggest that the hyperparathyroidism associated with a high level of i-PTH has no marked influence on bone density and elasticity. However, a previous study using absorptiometry in dialyzed patients found no correlation between i-PTH and bone osteopenia [17] and, as mentioned above, the patients with hyperparathyroidism had a higher BMD than the patients with osteomalacia [13]. Another study showed that BMD of the total body and arm was inversely correlated with i-PTH [18]. Unfortunately we are not always able to exclude the infuence of soft tissue calcification on the result of DXA at least. The serum ionized calcium and phosphorus levels were hardly correlated with the QUS and DXA results. We conclude that the duration of dialysis treatment, and especially the duration of CRF, correlate with the degree of osteopenia found with DXA and the disturbances in bone density and elasticity found with QUS. Among available biochemical parameters the activity of serum alkaline phosphatase and its bone fraction was the best predictor of bone changes evaluated by DXA and QUS.

Is the place of QUS in the diagnosis of renal osteodystrophy as a complementary technique to DXA or an alternative? In our comparisons between the two methods we saw them as alternatives. The answer to this question in the absence of histomorphometry is difficult. The different measurement sites and (according to the medical literature) rather different information that the two techniques provide, makes it difficult to take them as alternatives and suggests rather that one supplements the other. We think, however, that our data are too limited to solve this problem properly. The important advantages of QUS when compared with DXA are the smaller and portable device, lack of ionizing radiation, simplicity of use and lower cost. To identify the real clinical significance of QUS in the treatment and prophylaxis of bone disorders in patients with ESRF treated with dialysis needs further investigation.

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