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Original Article

Skeletal Status in Children, Adolescents and Young Adults with End-Stage Renal Failure Treated with Hemo- or Peritoneal Dialysis

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Abstract. The skeletal status in 30 children, adolescents and young adults (18 females, 12 males) with end-stage renal failure (ESRF) aged 9-23 years (mean 15.8 ± 3.6 years) was evaluated using measurements of bone mineral density (BMD, g/cm^2) at the spine and total body (TB) (Lunar DPX-L, USA), quantitative ultrasound (QUS) of the hand phalanges (DBM Sonic 1200, IGEA, Italy) and laboratory investigations (parathyroid hormone, serum total and ionized calcium, serum phosphate). Eleven subjects were treated with hemodialysis and 19 with peritoneal dialysis. The mean value of the amplitude-dependent speed of sound (Ad-SoS, m/s) measured by QUS was significantly decreased in comparison with the value obtained in a group of 686 age-matched controls (1942 ± 74 m/s vs 2050 ± 77 m/s, $p<0.0001$). BMD measurements were also decreased in comparison with mean values for the healthy population (Z-scores for spine −1.47, and for TB −1.53). Duration of dialysis correlated significantly with spine-BMD, TB-BMD and Ad-SoS ($r = -0.37$, $r = -0.45$, $r = -0.55$, respectively, $p<0.05$), while duration of ESRF did not have such an influence. Laboratory investigations did not correlate with skeletal parameters. Ad-SoS correlated significantly with spine-BMD ($r = 0.45$, $p<0.05$) and TB-BMD ($r = 0.56$, $p<0.01$). Both QUS and BMD values correlated significantly with Tanner stages (r ranged from 0.59 to 0.69, $p<0.001$) and did not increase with age except for correlation between age and TB-BMD. In conclusion, skeletal status in the population studied is strongly affected by ESRF. Both QUS and BMD measurements show an ability to express skeletal changes in a similar manner, though the QUS parameter seems to be more sensitive at revealing changes due to renal failure.

Keywords: Adolescents; Bone mineral density; Children; End-stage renal failure; Quantitative ultrasound; Young adults

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Introduction

Renal osteodystrophy is one of the most important complications of chronic renal failure, and bone loss is frequently seen already in the early phase of the disease [1]. Renal osteodystrophy may result in considerable morbidity for patients with end-stage renal failure (ESRF). Bone biopsy with tetracycline labeling is still considered the 'gold standard' for the assessment of renal osteodystrophy [2,3]. Bone biopsy, being an invasive method, can not be widely used for assessing the skeletal status in subjects with ESRF. Lately, bone mineral density (BMD) measurements have more often been applied for the diagnosis of renal osteodystrophy [4–6]. More recently, quantitative ultrasound (QUS) methods were introduced for the diagnosis of skeletal changes due to ESRF [4,7–11]. QUS measurements can be performed in several sites of the skeleton, the most common being the calcaneus. In 1992 a new ultrasound (US) technology was developed for measurements of the

hand phalanges (DBM Sonic 1200, IGEA, Carpi, Italy). In some studies [4,7,8] these measurements allowed the detection of skeletal alterations in ESRF.

The aim of the present study was the evaluation of skeletal status in children, adolescents and young adults with ESRF using BMD measurements, QUS of the hand phalanges and laboratory investigations.

Subjects and Methods

Subjects

The study group consisted of 30 patients (18 females, 12 males) and 686 controls (423 females, 263 males). The clinical characteristics of the patients and controls are given in Table 1. The population studied included all subjects (children, adolescents, young adults) with ESRF from the Silesian region of Poland with about 4 million inhabitants. Eleven patients were treated with regular hemodialysis, receiving two or three dialysis sessions per week; the duration of hemodialysis was 6–15 h per week. Nineteen patients were on peritoneal dialysis (18 on automatic peritoneal dialysis and 1 on continuous ambulatory peritoneal dialysis). The average duration of renal replacement therapy was 3.1 $\pm$ 2.5 years, and the mean time since the diagnosis of chronic renal failure (CRF) was 6.2 $\pm$ 4.1 years. All subjects remained on drug therapy for CRF receiving calcium carbonate, 1α-hydroxycholecalciferol and erythropoietin. Ten subjects received corticosteroid therapy: 5 patients before the study, and 5 during the study. The mean duration of this treatment was 60 months (range 2–169 months), and the dose was 0.5–1 mg of prednisone per 1 kg of body weight daily. The reasons for CRF were: chronic pyelonephritis in 11 patients, chronic glomerulonephritis in 6, lupus nephritis in 2, polycystic kidney disease in 2, rapidly progressive glomerulonephritis, familial nephronophthisis, bilateral renal hypoplasia, Wegener's granulomatosis, amyloidosis, congenital nephrotic syndrome and toxic injury in 1 each, and unknown causes in 2. Sexual maturity was assessed using Tanner stages. There were 5 subjects without any symptoms of puberty, 4 in Tanner stage I, 3 in Tanner stage II, 3 in Tanner's stage III, 9 in Tanner stage IV and 5 in Tanner stage V. No past fractures were noted in the dialysis patients.

Table 1. Clinical characteristic of patients and controls

	Patients (n = 30)[a]	Controls (n = 686)[b]
Age (years)	15.8 $\pm$ 3.6	15.83 $\pm$ 3.24
Weight (kg)	43.4 $\pm$ 13.5	163.8 $\pm$ 13
Height (cm)	147.1 $\pm$ 17.1	54.9 $\pm$ 15
Duration of CRF (years)	6.2 $\pm$ 4.1	–
Duration of dialysis (years)	3.13 $\pm$ 2.53	–
Tanner stages	2.8 $\pm$ 1.82	3.7 $\pm$ 1.1

Values are mean $\pm$ SD.
CRF, chronic renal failure.
[a] Eighteen females, 12 males.
[b] Four hundred and twenty-three females, 263 males.

The control group for QUS examinations was recruited randomly from pupils of local schools and students of the Silesian School of Medicine. Prior to and during the evaluation there were no factors in the controls known to affect bone metabolism (either medications or diseases). The controls were selected from a group of 1010 subjects and matched with the patients for age and gender. It was not possible to obtain a control group comparable with the patients with regard to weight and height because the patients in ESRF had a mean body size much lower than the normal, healthy population. The local ethics committee gave its permission for the study protocol.

Methods

Skeletal status was assessed by dual-energy X-ray absorptiometry (DXA) examinations of the spine BMD (spine-BMD, g/cm^2) and total body BMD (TB-BMD, g/cm^2) using a DPX-L densitometer (Lunar, Madison, WI) and by US measurements of the proximal hand phalanges using a DBM Sonic 1200 (IGEA, Carpi, Italy). Comparison between BMD values in patients and in the normal, healthy population was provided using Z-scores. All DXA measurements were done by the same operator. The coefficient of variation (CV % = SD/mean $\times$ 100%) for BMD measurements was 1.1% for spine-BMD and 0.6% for TB-BMD.

The US unit consists of two probes mounted on an electronic caliper: one emitter and one receiver. The latter records the US energy after it has crossed the phalanx. We determined the amplitude-dependent speed of sound (Ad-SoS, m/s) in the distal metaphyses of the proximal phalanges of the second through fifth fingers of the dominant hand. As was previously shown, no statistically significant differences between measurements of the extremity with and without a fistula exist [5]. Speed of sound in bone tissue was calculated considering the first signal with an amplitude of 2 mV at the receiving probe; thus, the measured speed of sound is amplitude-dependent. Acoustic coupling was achieved using a standard US gel. All measurements were done by the same operator. The CV% was 0.64%.

The following laboratory tests were performed: serum intact parathyroid hormone (i-PTH), phosphorus and total and ionized calcium serum concentrations. All blood samples were taken just before hemodialysis, or in the morning in the patients treated with peritoneal dialysis.

Statistics

All calculations of means and standard deviations (SDs) as well as linear correlations were done using the Statistica program run on an IBM PC. Correlations between Tanner stages and skeletal values were performed using the Spearman rank correlation test. Because of the small size of the population studied we

did not calculate statistical relationships separately for gender and for the type of dialysis; all analyses were performed for whole group. Statistical significance was achieved with $p<0.05$.

Results

Table 2 shows the results of bone measurements and laboratory data in patients. BMD of the spine and total body are expressed in grams per square centimeter and *Z*-scores. Such data allow comparison of our results with normal values for age and gender.

Ad-SoS was significantly lower in the dialysis patients in comparison with controls (1942 ± 74 m/s vs 2050 ± 77 m/s, $p<0.0001$). Also BMD values were decreased in comparison with the normal healthy population (*Z*-score for spine-BMD was −1.47 and for TB-BMD was −1.53). Ad-SoS correlated significantly with spine-BMD ($r = 0.45$, $p<0.05$) and TB-BMD ($r = 0.56$, $p<0.01$), and spine- and TB-BMDs correlated with each other ($r = 0.81$, $p<0.0001$). The mean value of i-PTH was increased in the dialysis patients, while serum total and ionized calcium, and phosphate, were in the normal range. Correlations of skeletal measurements with laboratory data were calculated and no significant relationships were obtained except for the correlation between ionized calcium and spine-BMD ($r = -0.37$, $p = 0.05$). i-PTH showed a weak, negative, nonsignificant correlation with Ad-SoS ($r = -0.29$, $p = 0.13$). Skeletal measurements were also correlated with the duration of renal failure, duration of dialysis, age, weight, height and Tanner stages. These data are presented in Table 3. All three bone parameters correlated negatively and significantly with duration of dialysis, though the Ad-SoS value was affected more than the BMD values. Duration of CRF did not correlate with Ad-SoS and BMD of the spine and TB. Age correlated significantly and positively with TB-BMD, while spine-BMD and Ad-SoS showed a weaker, nonsignificant positive relationship with age. In the controls, Ad-SoS correlated significantly with age ($r = 0.73$, $p<0.0001$). Weight, height and data expressing sexual maturation assessed by Tanner stages correlated significantly with all three skeletal parameters in dialysis patients.

Table 2. Results for skeletal and laboratory measurements in patients with end-stage renal failure

Spine-BMD	0.909 ± 0.23
Age-matched	86.6 ± 20.1
Z-score	−1.47 ± 2.15
TB-BMD	0.928 ± 0.12
Age-matched	88.6 ± 10.4
Z-score	−1.53 ± 1.42
Ad-SoS (m/s)	1942 ± 74
i-PTH (pg/ml)	327 ± 342
Total serum calcium (mmol/l)	2.46 ± 0.23
Ionized serum calcium (mmol/l)	1.15 ± 0.08
Phosphorus (mmol/l)	1.77 ± 0.64

Values are mean ± SD.
TB, total body; Ad-SoS, amplitude-dependent speed of sound; i-PTH, intact parathyroid hormone.

Discussion

The study has shown the serious abnormalities of skeletal status in the population studied. To our knowledge no studies using BMD and QUS measurements in persons with ESRF aged less than 17 years have previously been published. Generally, there is a significantly greater number of adults than young subjects with ESRF treated with dialysis. In 1998 in the whole of Poland 6878 persons were on dialysis [12]. Among them 242 subjects were younger than 20 years. This means that our group constitutes of about 12% of Polish dialysis patients (we had only 2 subjects older than 20 years). Because of the lack of other data it is not possible to compare current results with other studies performed in subjects of a comparable age. Results of QUS measurements in our study were compared with data for a large sample of the control group and have shown that skeletal status in our subjects is strongly affected by the disease. The difference between Ad-SoS in patients and controls was 108 m/s and this difference expressed in standard deviations is 1.45 (calculated as 108 m/s; 74 m/s is the SD value in the dialysis patients), which is very close to the *Z*-scores obtained for spine- and TB-BMDs in our population. In the study by Rico et al. [8] performed with a DBM Sonic, a difference

Table 3. Correlations between skeletal parameters and age, body size, durations of chronic renal failure and dialysis, and Tanner stages

	Age (years)	Weight (kg)	Height (cm)	Duration of CRF (years)	Duration of dialysis (years)	Tanner stages
Spine-BMD (g/cm^2)	0.33 (NS)	0.51 (<0.01)	0.62 (<0.001)	0.04 (NS)	−0.37 (<0.05)	0.69 (<0.0001)
TB-BMD (g/cm^2)	0.4 (<0.05)	0.74 (<0.0001)	0.69 (<0.001)	−0.12 (NS)	−0.45 (<0.05)	0.63 (<0.001)
Ad-SoS (m/s)	0.29 (NS)	0.4 (<0.05)	0.53 (<0.01)	−0.21 (NS)	−0.55 (<0.01)	0.59 (<0.001)

Values are correlation coefficients (r), with p values in parentheses. CRF, chronic renal failure; TB, total body; Ad-SoS, amplitude-dependent speed of sound.
NS, not significant.

between hemodialyzed patients and controls expressed in *Z*-scores was about 1. In another study investigating US propagation in the hand phalanges [10] in hemodialysis patients the difference between the value for healthy controls and patients was 119 m/s. If the latter value were expressed as a *Z*-score it would be −1.4, which is very close to our data. A greater reduction in *Z*-score was observed by Foldes et al. [11] for speed of sound at the tibia (−2.0), which can probably be explained by the fact that cortical bone is more sensitive to the influence of an increase in i-PTH level.

Also important information is provided by the comparison of age-related increase in Ad-SoS in the dialysis patients with the same relationships in controls. In subjects with ESRF Ad-SoS did not increase significantly with age, while in controls this correlation is significant ($r = 0.73$, $p<0.0001$). This means that we can expect the peak value of Ad-SoS in a patient with ESRF to be lower than in healthy, control subjects. Correlations between age and BMD measurements provide a similar result. Only TB-BMD increased significantly with age in our subjects. In the study by Sabatier et al. [13] performed in a large population of 574 persons aged 10–24 years, spine BMD correlated significantly with age ($r = 0.49$). Even stronger relationships were reported by Bonjour et al. [14] who obtained, in a population of 207 young subjects aged 9–18 years, correlations of spine BMD with age of 0.78 for males and 0.8 for females, and 0.63–0.87 and 0.7–0.84, respectively for hip BMD. Our nonsignificant correlation of spine-BMD with age ($r = 0.33$) is weaker than those obtained in these other studies. We did not find any study presenting a correlation between TB-BMD and age, so direct comparison is not possible. Only Zanchetta et al. [15] in a study performed in a cohort of 900 subjects aged 2–20 years assessed whole body mineral content. In this study, however, no exact value of correlation between age and whole body mineral content was presented, despite the fact that this relationship was significant. On the basis of our data we suspect that neither spinal nor total body peak BMD in subjects with ESRF will reach the level attained in a normal, healthy population. This may result in increased fracture risk in this population in the future. These observations concerning BMD are very similar to those obtained for our US parameter.

Correlations between skeletal and laboratory measurements did not show any significant relationships, but the correlation coefficient between Ad-SoS and i-PTH ($r = -0.29$) is almost the same as that obtained in the study by Montagnani et al. [7], who noted $r = -0.28$ with $p<0.05$. Probably the smaller size of our group prevented the correlation reaching significance. A slightly stronger significant inverse correlation was noted by Foldes et al. [11] between tibial SOS and i-PTH ($r = -0.39$, $p<0.01$).

It is interesting to compare the current data with results obtained by Przedlacki et al. [4]. In this study the same device for US measurements was used, and also some DXA evaluations were done (hand, ultradistal radius, radial shaft) in a group of adults with ESRF. Correlations between US and BMD measurements were higher ($r = 0.46$–0.68) than in our study ($r = 0.45$–0.55), which can probably be explained by the similar cortical/trabecular ratio in sites measured in this study. The duration of dialysis correlated with QUS ($r = -0.41$) and BMD values ($r = -0.35$ to -0.53), which is very close to our data, and duration of renal failure significantly affected both US and BMD values, which was not observed in the current study. Some differences were noted in the comparison of current relationships between i-PTH and skeletal parameters; we did not find such connections, while in Przedlacki et al.'s study i-PTH correlated significantly with Ad-SoS in men ($r = -0.54$), and with DXA of the hand ($r = -0.38$) and radial shaft ($r = -0.49$). In the study by Przedlacki et al. ionized calcium correlated significantly with Ad-SoS only, while in the current study only spine-BMD was correlated significantly with serum ionized calcium. The lack of significant correlations between i-PTH and skeletal parameters may suggest that hyperparathyroidism associated with a high level of i-PTH has no marked influence on bone status in our patients. A similar observation is derived from the study in which no correlation between i-PTH and bone osteopenia was found [16]. Another study showed that BMD of the total body and arm were inversely correlated with i-PTH [17].

The limitations of our study were: (1) the lack of analyses performed separately for gender and type of dialysis, due to the relatively small sample size, and (2) the cross-sectional design. Despite these limitations it can be concluded that skeletal status in the population studied is strongly affected by ESRF. Both QUS and BMD measurements show an ability to express skeletal changes in a similar manner, though the QUS parameter seems to be more sensitive to changes due to renal failure because of a stronger negative relationship between Ad-SoS and duration of dialysis.

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