

Skeletal status in children and adolescents with chronic renal failure before onset of dialysis or on dialysis

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Abstract Bone status was assessed in 15 children and adolescents with predialysis chronic renal failure (CRF) and in 25 subjects with end-stage renal failure (ESRF). The mean age in the whole group was 14.6 ± 3.2 years and CRF had been recognized 5.8 ± 4.0 years earlier. The mean age, body size, duration of the disease and Tanner stages did not differ significantly between patients with predialysis CRF and ESRF. The control group consisted of 890 healthy subjects matched with patients for age. Bone mineral density (BMD) was measured by DPX-L (Lunar, Madison, WI) at the spine (s-BMD) and total body (TB-BMD); quantitative ultrasound (QUS) was performed by DBM 1200 (IGEA, Italy) at the hand phalanges (Ad-SoS). Laboratory investigations included the evaluation of intact parathyroid hormone (i-PTH), total and ionized serum calcium, and serum phosphate. In the whole group of patients the following mean values were obtained: Ad-SoS 1952 ± 79 m/s (significantly lower than in controls, who had Ad-SoS 2022 ± 85 m/s,

$p < 0.05$; the difference remained significant after adjusting for body mass index), s-BMD 0.87 ± 0.22 g/cm² (Z-score -1.6), TB-BMD 0.92 ± 0.12 g/cm² (Z-score -1.44), i-PTH 276 ± 300 pg/ml, total calcium 2.46 ± 0.19 mmol/l, ionized calcium 1.14 ± 0.08 mmol/l, phosphate 1.68 ± 0.61 mmol/l. Skeletal measurements correlated significantly with age, body size and Tanner stages (also after adjusting for age), while significant correlations of these parameters with the duration of CRF and laboratory investigations (except of correlations of i-PTH with Ad-SoS and with TB-BMD in predialysis patients) were not observed. None of the studied variables differed significantly between predialysis and dialysis patients. In conclusion, both predialysis and dialysis children and adolescents showed a decrease in BMD and quantitative ultrasound measurements. The severity of skeletal alterations was similar in the early phase (predialysis patients) and end stage (dialysis patients) of the disease and did not show a tendency to progress with CRF duration.

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Introduction

Chronic renal failure (CRF) is associated with skeletal changes known as renal osteodystrophy, including different types of bone tissue abnormalities when assessed by histomorphometry [1, 2, 3]. Bone abnormalities are present in the late stages of CRF, and patients with mild to moderate degrees of CRF rarely experience symptoms [4]. However, some studies have shown that more than 50% of patients with mild to moderate renal failure have abnormal bone histology [1, 5]. Such data suggest that skeletal changes may occur many years before the symptoms arise and, at least in some patients, in the very early stages of CRF [4]. Studies on skeletal changes due to CRF

are generally performed in patients on dialysis [6, 7] and only a few studies involving patients with mild to moderate CRF (before dialysis) have been published [4, 8]. Only some studies were performed in children with CRF [9]. Histomorphometry, being an invasive technique, cannot be widely used in clinical practice, and especially in a pediatric population such methodology ought to be used with caution. The severity of skeletal changes in the course of CRF is usually evaluated by BMD measurements and laboratory investigations [6, 10, 11]. More recently, a new technique based on QUS has been developed and in several studies patients with CRF were evaluated using this method [6, 9, 11, 12, 13, 14, 15]. The authors have demonstrated that calcaneal [11], tibial [12] and phalangeal [6, 9, 13, 14, 15] ultrasound parameters are a useful tool in the assessment of skeletal changes in patients with CRF. The lack of ionizing radiation is a very important feature of QUS that makes this method especially useful in a pediatric population.

In the present study a group of children and adolescents with CRF before dialysis and with ESRF have been evaluated. Skeletal changes may lead to fragility fractures in patients with CRF and early detection of bone abnormalities may be helpful in patient management. On the other hand, aggressive parathyroid hormone suppression has led to the increased prevalence of adynamic bone disease.

To our knowledge, no studies on skeletal changes in predialysis stages of CRF in children and adolescents using both QUS and BMD have been published previously.

Subjects and methods

Forty subjects (22 females, 18 males) with CRF from the Silesia district were evaluated. The group included 25 patients on dialysis (14 females, 11 males) and 15 predialysis patients (8 females, 7 males). The causes of CRF were: chronic pyelonephritis in 17 cases (9 in the subgroup of patients on dialysis + 8 in the subgroup of predialysis patients), chronic glomerulonephritis in 9 cases (6 + 3), lupus nephritis in 2 cases (2 + 0), polycystic kidney disease in 2 cases (1 + 1), amyloidosis in 2 cases (1 + 1), familial nephronophthisis in 1 case (1 + 0), interstitial nephritis in 1 case (1 + 0), bilateral renal hypoplasia in 1 case (1 + 0), Wegener's granulomatosis in 1 case (1 + 0), congenital nephrotic syndrome in 1 case (1 + 0), cystinosis in 1 case (0 + 1), hemolytic-uremic syndrome in 1 case (0 + 1) and an unknown cause in 1 case (1 + 0).

In the subgroup of patients on renal replacement therapy there were 9 subjects treated with regular hemodialysis and 16 subjects on peritoneal dialysis. All the patients of both subgroups remained on conservative drug treatment for CRF comprising calcium supplementation (calcium carbonate, calcium gluconate) and administration of active vitamin D₃ derivatives (alfacalcidol, GlaxoSmithKline). Fourteen patients were receiving or had previously received glucocorticosteroids (GCS): 9 in the subgroup of patients on dialysis and 5 in the subgroup of predialysis patients. Mean age, weight, body mass index (BMI) and height in subjects taking GCS did not differ significantly in comparison with subjects without such treatment (data not shown).

Sexual maturity was assessed using Tanner stages. Table 1 presents the patients' clinical data. Mean age, weight, height, Tanner stages and duration of CRF did not differ significantly between predialysis and dialysis patients.

Table 1 Clinical characteristics of subjects studied

	Mean \pm SD	Range
<i>All patients (n = 40)</i>		
Age (years)	14.6 \pm 3.2	7.6–19.1
Weight (kg)	40.05 \pm 12.4	17.0–76.0
Height (m)	1.45 \pm 0.17	1.06–1.78
BMI (kg/m ²)	18.68 \pm 3.15	14.60–27.27
Tanner stage	2.92 \pm 1.65	1.0–5.0
CRF duration (years)	5.8 \pm 4.0	0.1–13.8
<i>Predialysis patients (n = 15)^a</i>		
Age (years)	14.2 \pm 3.4	7.6–18.1
Weight (kg)	37.6 \pm 12.1	17.0–55.0
Height (m)	1.43 \pm 0.19	1.06–1.71
BMI (kg/m ²)	17.88 \pm 2.41	15.13–22.96
Tanner stage	3.0 \pm 1.85	1.0–5.0
CRF duration (years)	5.6 \pm 3.9	1.0–13.5
<i>Dialysis patients (n = 25)^a</i>		
Age (years)	14.9 \pm 3.2	8.8–19.1
Weight (kg)	41.5 \pm 12.6	25.0–76.0
Height (m)	1.46 \pm 0.17	1.10–1.78
BMI (kg/m ²)	19.17 \pm 3.47	14.60–27.27
Tanner stage	2.88 \pm 1.56	1.0–5.0
CRF duration (years)	6.0 \pm 4.1	0.1–13.8
<i>Control group (n = 890)</i>		
Age (years)	14.6 \pm 3.7	6.5–23.0
Weight (kg)	50.2 \pm 15.9	17.1–100.0
Height (m)	1.59 \pm 0.15	1.13–1.95
BMI (kg/m ²)	19.6 \pm 3.4	12.3–33.2

^aNo significant differences between predialysis and dialysis patients

The control group for the QUS examination was recruited randomly from pupils of local schools. This group consisted of 890 subjects. The clinical characteristics of the control group are also presented in Table 1. The control group was selected from 1,010 subjects and matched with patients (all patients, predialysis and dialysis patients) for age and gender. It was not possible to obtain a control group comparable with patients with regard to weight and height because patients with CRF had a mean body size much lower than the normal, healthy population. In the control group only QUS measurements were performed. Prior to and during the evaluation no factors known to affect bone metabolism (medications or diseases) were present in the controls. In the controls Tanner stages were not assessed.

The local ethics committee gave permission for the study.

Skeletal status was assessed by dual-energy X-ray absorptiometry (DXA) and by QUS of hand proximal phalanges. DXA measurements of BMD (g/cm²) of the lumbar spine (s-BMD) and total body (TB-BMD) were performed with a Lunar DPX-L (Lunar, Madison, WI). The BMD results were compared with a reference population and expressed as Z-scores as well. The coefficient of variation (CV% = SD/mean \times 100%) for BMD measurements was 1.1% for the spine and 0.6% for total body.

QUS was performed with a DBM Sonic 1200 (IGEA, Italy), measuring amplitude-dependent speed of sound (Ad-SoS, m/s) in the proximal phalanges of fingers II–V of the right hand. The coefficient of variation (CV%) based on 60 measurements performed in 12 patients with renal failure aged 10–19 years (5 scans for each of them) was 0.61%.

All the patients also had laboratory parameters of calcium and phosphate metabolism measured. The levels of total calcium and phosphate were determined using a Kodak Ektachem 700XR device and the level of ionized calcium was measured by AVL 984 S analyzer. The serum level of i-PTH was measured by radioimmunoassay (Biosource, Belgium).

Statistical analysis was performed using Student's *t*-test for independent samples, Mann-Whitney *U*-test (in the case of non-parametric data and a non-normal distribution), Pearson linear correlation test and Spearman rank correlation test. All results were considered as statistically significant at *p* < 0.05.

Results

Table 2 presents the densitometric, ultrasound and laboratory results in the patients. Ad-SoS was significantly lower in all patients and in both subgroups than in the controls, who had an Ad-SoS value of 2022 ± 85 m/s ($p < 0.001$). This difference was also significant after adjusting for BMI ($p < 0.01$). Spine and total body BMDs expressed as Z-scores were lower than in the normal healthy population and ranged from -1.4 to -2.0 for s-BMD, and from -1.37 to -1.49 for TB-BMD. No statistically significant differences between patient subgroups were noted with regard to BMD, Ad-SoS and values of laboratory investigations. Table 3 gives the results of correlation analyses of BMD and QUS measurements with other variables in predialysis and dialysis patients. Skeletal variables correlated significantly with age and body size while no significant correlations with duration of CRF and laboratory investigations (except for correlations of i-PTH with Ad-SoS and TB-BMD in predialysis patients) were observed. i-PTH did not correlate with the duration of the disease in the whole group, in predialysis patients, in dialysis patients or in a group of patients on GCS. In patients with ESRF the

duration of the dialysis correlated significantly and negatively with TB-BMD ($r = -0.48$, $p < 0.05$). Correlations between Ad-SoS and BMD measurements are presented in Table 4. Ad-SoS correlated significantly with spine BMD and TB-BMD but stronger correlations were observed with TB-BMD. Spearman correlations of skeletal measurements with Tanner stages are presented in Figs. 1 and 2. All these correlations were significant ($p < 0.01$) and remained significant after adjusting for age (in the whole group: Ad-SoS $r = 0.52$, $p < 0.001$; spine BMD $r = 0.50$, $p < 0.001$; TB-BMD $r = 0.47$, $p < 0.001$). The laboratory values were compared with values in the normal healthy population. Serum total and ionized calcium were in the normal range, phosphate was slightly increased and i-PTH was about 3 times greater than the upper normal limit.

Discussion

In the current study skeletal abnormalities in patients with CRF were observed. The presence of decreased BMD and diminished values of an ultrasound parameter in the late stages of the disease could be expected, but

Table 2 Results of BMD and QUS measurements and laboratory investigations

	Mean \pm SD		
	All patients	Predialysis patients	Dialysis patients
Spine BMD (g/cm ²)	0.867 ± 0.22	0.808 ± 0.24	0.903 ± 0.21
Z-score	-1.62 ± 1.95	-2.0 ± 1.66	-1.4 ± 2.11
Total body BMD (g/cm ²)	0.919 ± 0.12	0.908 ± 0.14	0.925 ± 0.11
Z-score	-1.44 ± 1.3	-1.37 ± 0.99	-1.49 ± 1.48
Ad-SoS (m/s)	$1,952 \pm 79$	$1,958 \pm 101$	$1,949 \pm 65$
PTH (pg/ml)	276 ± 300	235 ± 187	291 ± 335
Total serum calcium (mmol/l)	2.46 ± 0.19	2.5 ± 0.15	2.43 ± 0.22
Ionized serum calcium (mmol/l)	1.14 ± 0.08	1.14 ± 0.09	1.14 ± 0.08
Serum phosphate (mmol/l)	1.68 ± 0.61	1.52 ± 0.45	1.78 ± 0.68

Table 4 Correlations between Ad-SoS and BMD measurements

	Ad-SoS (m/s)	Spine BMD (g/cm ²)
<i>All patients (n = 40)</i>		
Spine BMD (g/cm ²)	0.59 $p < 0.0001$	–
Total body BMD (g/cm ²)	0.71 $p < 0.0001$	0.82 $p < 0.0001$
<i>Predialysis patients (n = 15)</i>		
Spine BMD (g/cm ²)	0.76 $p < 0.01$	–
Total body BMD (g/cm ²)	0.83 $p < 0.0001$	0.90 $p < 0.0001$
<i>Dialysis patients (n = 25)</i>		
Spine BMD (g/cm ²)	0.49 $p < 0.05$	–
Total body BMD (g/cm ²)	0.60 $p < 0.01$	0.78 $p < 0.0001$

Table 3 Correlations of BMD and QUS measurements with other variables in predialysis patients ($n = 15$) and dialysis patients ($n = 25$)

		Age (years)	Weight (kg)	Height (m)	CRF duration (years)	Dialysis duration (years)	i-PTH (pg/ml)
Ad-SoS (m/s)	Predialysis	0.75 $p < 0.01$	0.85 $p < 0.001$	0.91 $p < 0.001$	–0.05 NS		–0.67 $p < 0.05$
	Dialysis	0.76 $p < 0.001$	0.41 $p < 0.05$	0.5 $p < 0.05$	0.04 NS	–0.31 NS	–0.24 NS
Spine BMD (g/cm ²)	Predialysis	0.71 $p < 0.01$	0.87 $p < 0.001$	0.80 $p < 0.001$	–0.01 NS		–0.45 NS
	Dialysis	0.51 $p < 0.01$	0.43 $p < 0.05$	0.58 $p < 0.01$	0.18 NS	–0.25 NS	0.04 NS
Total body BMD (g/cm ²)	Predialysis	0.83 $p < 0.001$	0.96 $p < 0.001$	0.91 $p < 0.001$	0.07 NS		–0.75 $p < 0.05$
	Dialysis	0.57 $p < 0.01$	0.74 $p < 0.0001$	0.67 $p < 0.001$	–0.03 NS	–0.48 $p < 0.05$	–0.11 NS

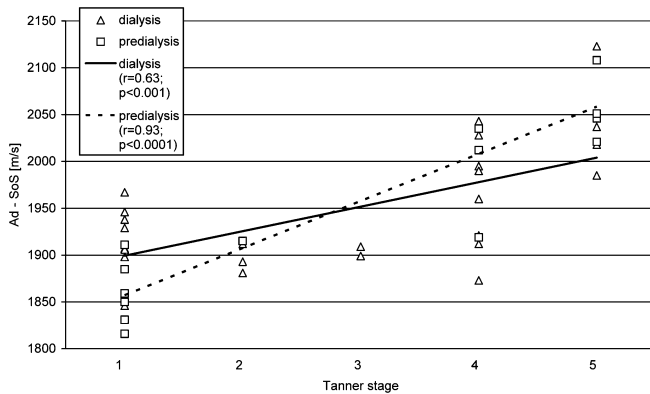


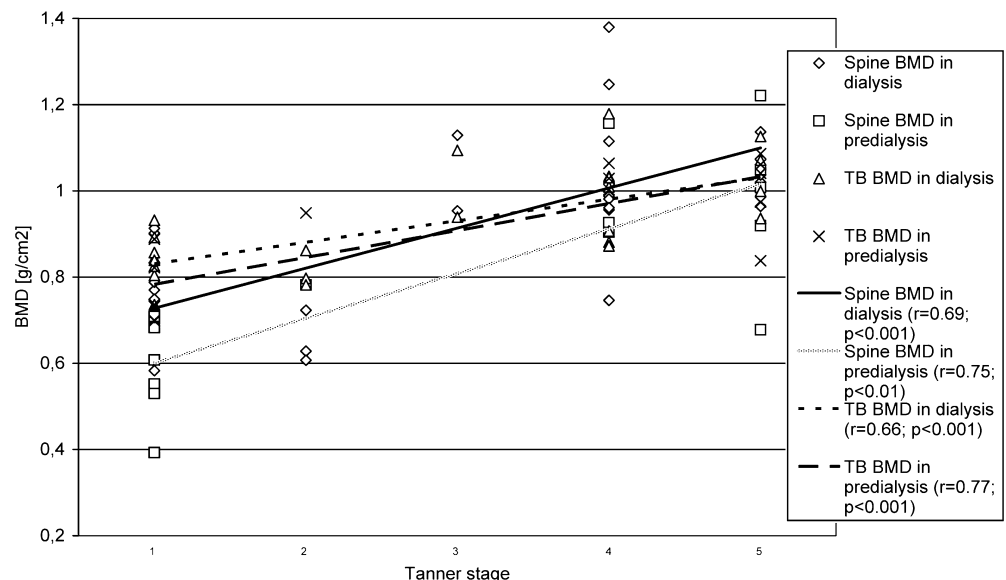
Fig. 1 Spearman correlations of Tanner stages with ultrasound measurements

the decrease was also noted in predialysis patients. To our knowledge, no studies on skeletal changes in predialysis stages of CRF in children and adolescents using both QUS and BMD have been published previously. Since no statistical differences between dialysis and predialysis patients in bone variables occurred, the results of our study confirm the hypothesis that skeletal changes may be initiated in predialysis patients and QUS is able to reveal them. These observations seem to be the most important result of the study.

Particularly interesting is the possibility of the application a safe ultrasound method in young subjects with CRF. The lack of ionizing radiation supports the value of QUS. Other advantages, such as the portability of devices, their relatively low cost and the short time required to perform scans at the hand phalanges, ought to be taken into consideration also. Ad-SoS seems to be a very promising parameter since the high content of cortical bone at the measurement site may express the influence of secondary hyperparathyroidism in the

course of CRF. The disadvantage of using QUS in young patients with CRF is the limited amount of data presented by other authors, which makes clinically valuable comparisons difficult. There have been no published longitudinal studies on the use of QUS. Such studies would be helpful to provide further data. In our center such a prospective study is currently in progress. QUS measurements have been performed in patients with CRF in numerous studies [6, 9, 11, 12, 13, 14, 15], but in all these investigations, except for our recent study [9], only adult subjects were evaluated and direct comparisons cannot be carried out. Correlation analysis between BMD and QUS variables provides interesting data. Ad-SoS measured at the hand phalanges, which mostly consist of cortical bone, correlated more strongly with TB-BMD (mainly cortical bone) than with s-BMD (50% trabecular bone). This result suggests that cortical skeletal sites may be more appropriate in the assessment of bone changes in patients with CRF. This hypothesis is supported also by the observation of Bianchi et al. [8], who noted a decrease in BMD only in cortical bone. Cortical bone is more sensitive to i-PTH, and in other studies Ad-SoS correlated with i-PTH. In Montagnani et al.'s study [14] the correlation coefficient was -0.29 ($p < 0.05$). A slightly stronger inverse correlation was noted by Foldes et al. [12] between tibial Ad-SoS and i-PTH ($r = -0.39$, $p < 0.01$). In the current study inverse, significant correlations of i-PTH with Ad-SoS and TB-BMD were noted only in predialysis patients. This confirms that cortical bone is more sensitive to an increased level of i-PTH. These correlations are present despite the fact that i-PTH did not show any tendency to drop with duration of the disease. These results may suggest that cortical sites are rather sensitive in the early stages of the disease. Perhaps the lack of correlation between measured parameters and i-PTH in the whole group and dialysis patients may also be explained by the influence of concomitant treatment, especially the

Fig. 2 Spearman correlations of Tanner stages with BMD measurements



administration of alfacalcidol. Vitamin D₃ and its active derivatives cause the suppression of i-PTH secretion, but the effect of such treatment on bone tissue is not immediate. The lack of differences between data in patients with and without GCS suggests that this therapy is not detrimental as might be expected in young patients with CRF. This unexpected finding requires further longitudinal observation.

In comparison with data provided by other authors [12, 14] one important factor ought to be taken into consideration. Namely, we observed in the current study that i-PTH did not correlate with CRF duration, while previous authors have not provided such data. Therefore, the inverse correlations noted by these authors may be caused by the progressive decrease in i-PTH. Stable values of i-PTH may also partly explain the stable values of Ad-SoS and BMD. Rix et al. [4] showed significant negative correlations of i-PTH with BMD Z-scores of the femur and forearm in predialysis adult patients. Other authors observed decreased values of BMD in children with ESRF [16]. If CRF occurs before skeletal maturity is reached an adequate peak bone mass may not be achieved. Therefore, subjects with CRF have an increased risk of developing osteopenia. In our study skeletal parameters correlated with Tanner stages and correlation coefficients ranging from 0.63 to 0.93 were obtained. These relationships remain significant also after adjusting for age. In some other studies skeletal parameters were correlated with sexual maturity assessed by Tanner stages. In a recent study by Baroncelli et al. [17] in a group of 1,083 healthy subjects aged 3–21 years the correlation between Ad-SoS and Tanner stages was 0.74 in males and 0.73 in females, which are in a similar range to the current study. In another study [18], conducted in 125 persons aged 9–25 years, both QUS measurements at the calcaneus and BMD measurements (total body, spine and femoral neck) were performed. The authors obtained correlation coefficients of Tanner stages with ultrasound parameters 0.37–0.75 and with BMD data of 0.47–0.72. We obtained comparable *r* values from 0.66 to 0.77. The comparisons of our results with other data on relationships between sexual maturity and skeletal parameters show a similar general tendency in their increasing parallel with increasing sexual maturity.

Some other authors have observed abnormal bone histology in patients with moderate CRF [1, 5]. In the study by Rix et al. [4], in a group of 113 predialysis patients, BMD was reduced in the axial and appendicular skeleton, indicating that both cortical and trabecular bone was affected. In the current study we also noted reduced spine and total body BMD. Bianchi et al. [8] obtained different results and observed a decrease only in cortical bone.

In our study mean age, body size and sexual maturation did not differ significantly between patient subgroups, which allowed for reliable comparison. Also, duration of renal failure was similar in predialysis and dialysis patients. Data concerning correlations of CRF duration with skeletal variables studied seem to be

especially important. Ad-SoS and BMD measurements did not show any tendency to decrease during CRF. This probably means that the skeletal changes occur early and that later bone status is rather stable. The analysis of the relationships between duration of CRF and skeletal variables may be also affected by difficulties in the precise assessment of disease onset and the influence of effective management of secondary hyperparathyroidism.

Our study has several limitations: the small sample of patients, a cross-sectional design, the lack of data on bone turnover and the estimation of Tanner stages in controls.

A longitudinal study in patients with CRF is in progress and the results of this study may give further important data.

In conclusion, both predialysis and dialysis children and adolescents show a decrease in BMD and QUS measurements. The severity of skeletal adverse effects was similar in the early stages (predialysis patients) and the end stages (dialysis patients) of the disease and did not show a tendency to progress with CRF duration.

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