

Skeletal status in adolescents with end-stage renal failure: a longitudinal study

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Abstract In a longitudinal study, bone status was assessed in adolescents and young adults aged 15.3 ± 3.4 years at the onset of the study with end-stage renal failure (ESRF). The group consisted of 18 subjects (11 females and seven males), of whom nine patients were on hemodialysis and nine patients on peritoneal dialysis. Six patients were previous or current glucocorticoid (GCS) users. Renal failure was recognized before 6.1 ± 4.1 years, and dialysis was performed for 3.0 ± 2.0 years. Follow-up took place 8.6 ± 0.8 and 21.7 ± 2.5 months later, and the following data were collected: bone mineral density (BMD) at the spine (s-BMD) and total body (TB-BMD) using DPX-L (Lunar, USA); quantitative ultrasound by DBM 1200 (IGEA, Italy) at the hand phalanges (Amplitude-dependent Speed of Sound, Ad-SoS), serum concentration of i-PTH, total calcium, ionized calcium and phosphate. Tanner stages were also evaluated. The mean values of BMD mea-

surements and Ad-SoS were stable during a period of observation, and a mean Z-score for TB-BMD was significantly lower at the third versus baseline value (-1.87 ± 1.75 versus -1.49 ± 1.53 , $P < 0.05$). Z-scores for s-BMD and Ad-SoS decreased non-significantly. Changes in s-BMD and TB-BMD Z-scores were influenced by changes in body size and changes in biochemical parameters, and a change in Ad-SoS Z-score was not dependent on these factors. The values of second ($P < 0.05$) and third ($P < 0.01$) s-BMD Z-score were significantly lower in GCS treated subjects, and longitudinal change in spine Z-score was greater in GCS treated patients versus others ($P < 0.05$). Duration of ESRF, duration and type of dialysis and gender did not influence skeletal variables. Skeletal measurements correlated significantly with Tanner stages (besides the correlation with Ad-SoS in the first measurement, r ranged from 0.5 to 0.72, $P < 0.05$), and changes in Tanner stages observed over a period of observation did not correlate with changes in skeletal variables. Among laboratory variables, the following non-significant tendencies to change were observed: serum concentration of i-PTH and phosphate increased, and total and ionized calcium decreased. In conclusion, adolescent subjects with ESRF treated with dialysis showed stable mean values of skeletal measurements, and these were expressed as Z-scores, a tendency to drop was observed. The lack of an increase observed in normal healthy subjects of the same age, and low values in Z-scores, indicates that skeletal status is seriously affected in subjects with ESRF.

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Introduction

End-stage renal failure (ESRF) is associated with skeletal changes known as renal osteodystrophy, including

different types of bone tissue abnormalities, when assessed by histomorphometry [1,2,3]. In several studies on skeletal changes caused by ESRF performed in patients on dialysis, serious changes in bone mineral density measurements [4,5,6,7,8] and laboratory parameters [4,5,7,8] were observed. More recently, a new technique based on quantitative ultrasound (QUS) was developed and in several studies patients with ESRF were evaluated using this method [5,7,8,9,10,11,12,13,14,15]. The authors have demonstrated that calcaneal [9,14,15], tibial [10] and phalangeal [5,7,8,11,12,13] ultrasound parameters are a useful tool in the assessment of skeletal changes in patients with renal failure. The lack of ionizing radiation is a very important feature of QUS, which makes this method especially useful in young individuals.

It is obvious that skeletal changes in ESRF may be more reliably assessed in longitudinal studies than in cross-sectional ones, but only some published studies have used this design [6,16,17,18]. In the current study, a group of young individuals with ESRF was evaluated longitudinally in order to detect changes occurring during renal insufficiency.

Materials and methods

Subjects

In the study 18 subjects (11 females and seven males) with ESRF from Upper Silesia conurbation were evaluated. The group included nine patients on hemodialysis and nine on peritoneal dialysis. Longitudinal observation was started in the group of 30 patients presented in our previous study [8]. The study was completed by 18 patients; 12 subjects were excluded during follow-up. The reasons for exclusion were: renal transplantation, eight patients, death, three and change of dialysis centre, one.

The causes of CRF were: chronic pyelonephritis in nine cases (five in the subgroup of patients on hemodialysis and four in the subgroup of patients on peritoneal dialysis), chronic glomerulonephritis in four (three and one), lupus nephritis in one (one and none), polycystic kidney disease in one (none and one), amyloidosis in one (none and one), familial nephronophytosis in one (none and one) and unknown cause in one (none and one).

All the patients from both subgroups remained on conservative drug treatment for CRF, comprising calcium supplementation (calcium carbonate, calcium gluconate) and administration of active vitamin D₃ derivatives (alfacalcidol). Among the group studied, three patients had previously received glucocorticosteroids (GCS) and three patients were currently taking GCS. Mean age and body size in subjects taking GCS did not differ significantly in comparison with subjects who had not taken GCS (data not shown).

Sexual maturity was assessed using Tanner stages. The local ethics committee gave permission for the study.

Methods

Skeletal status was assessed by dual-energy X-ray absorptiometry (DXA) and by quantitative ultrasound (QUS) of hand proximal phalanges. DXA measurements of areal bone mineral density [BMD (g/cm²)] of lumbar spine and total body were performed with Lunar DPX-L (USA). The results of BMD were compared with an age-matched reference population and also expressed as Z-scores. The coefficient of variation (CV% = SD/mean × 100%) for BMD measurements was 1.1% for spine and 0.6% for TB-BMD. Due to the lack of ethical approval to perform serial BMD measurements in ESRF, values of CVs were not obtained in patients with ESRF.

QUS was performed with DBM Sonic 1200 (IGEA, Italy), measuring amplitude-dependent speed of sound [Ad-SoS (m/s)] in 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 (five scans for each) was 0.61%. In order to calculate Z-score, values for Ad-SoS were used with normative data for QUS measurements performed in young individuals derived from the same region of the country.

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

Statistics

Statistical analysis was performed using Student's *t*-test for dependent samples, Pearson linear correlation test and Spearman rank correlation test. Due to the small number of males, all patients were analysed together. Changes in Z-score for skeletal variables noted over the period of the study were regressed in a multiple stepwise regression analysis on changes in body size and changes in biochemical parameters observed during the study. In order to follow reliable changes of Ad-SoS in individual subjects, the least significant change (LSC) was calculated. The LSC or critical difference denotes the minimum difference between two successive results in an individual that can be considered to reflect a real change. The LSC was calculated using the formula: CV% × 2 × 1.41, which would represent a statistical difference at the 95% confidence level [16]. Since precision was assessed in ESRF subjects only for Ad-SoS, the value of LSC was used only for changes in this parameter. All results were considered as statistically significant at *P* < 0.05.

Results

Physical characteristics of patients studied in three consecutive examinations are presented in Table 1. It is

Table 1 Clinical characteristics of subjects studied at baseline, at second and third measurement (mean \pm SD, for Tanner stages median with upper and lower quartile)

Mean value	Baseline \pm SD	Second measurement \pm SD	Third measurement \pm SD
Age (years)	15.3 \pm 3.4	16.0 \pm 3.4	17.1 \pm 3.5
Range (years)	8.8–20.0	9.4–20.7	10.7–21.9
Weight (kg)	42.8 \pm 15.6	42.8 \pm 13.4	42.7 \pm 10.5
Z-score	-1.08 \pm 1.7	-1.36 \pm 1.6	-1.79 \pm 1.4
Height (m)	1.46 \pm 0.2	1.48 \pm 0.16	1.5 \pm 0.15
Z-score	-2.5 \pm 2.7	-2.62 \pm 2.5	-2.72 \pm 2.8
Tanner stage	3.0 (1.0–4.0)	4.0 (2.0–4.0)	4.0 (2.0–5.0)
ESRF duration (years)	6.01 \pm 4.1	6.75 \pm 4.1	7.9 \pm 4.1
Dialysis duration (years)	2.97 \pm 2.0	3.64 \pm 2.0	4.79 \pm 2.1

important to note that children with ESRD are shorter and they have lower weight than a healthy age-matched population, which is expressed by negative Z-score values for height and weight. Those disturbances seem to be more pronounced with increasing length of renal replacement therapy. Among the group studied, there were ten subjects younger than 16 years, and during the period of the study, mean height increased significantly from 139.9 \pm 16.2 cm to 145.9 \pm 14.7 cm, and weight did not change.

Table 2 presents densitometric and ultrasound results in patients for baseline, second and third measurements. The mean values of BMD and Ad-SoS measurements were stable during the period of observation and no significant differences between them were noted. For Ad-SoS, using the LSC value both an increase and decrease was noted in four subjects. In Fig. 1, changes in Ad-SoS in individual patients are presented. Mean Z-score for TB-BMD was significantly lower at the third versus baseline value; Z-scores for s-BMD and Ad-SoS decreased non-significantly. In Fig. 2, a graphic presentation of mean Z-scores for densitometric and

ultrasound measurements is given. These findings suggest further deterioration in skeletal status relative to age. In Fig. 3, 4 and 5, changes in Z-scores in individual patients are presented.

The influence of GCS therapy on skeletal variables was established, comparing values in GCS treated patients (currently or previously) ($n=6$) and others ($n=12$) for baseline and follow-up measurements (Table 2). The only significant difference concerned the values of s-BMD Z-scores for second and third measurements, and Z-scores were lower in GCS treated patients (-0.76 ± 1.90 versus -2.37 ± 2.23 , NS for the first measurement; -0.76 ± 1.66 versus -2.76 ± 2.06 , $P < 0.05$ for the second measurement and -0.54 ± 1.74 versus -3.54 ± 2.07 , $P < 0.01$ for the third measurement). In order to show longitudinal changes in skeletal measurements, we also performed a correlation between Δ (difference between third and first measurement) for densitometric and ultrasound variables in steroid and non-steroid treated patients. Δ s-BMD Z-score was significantly lower in non-steroid patients (0.22 ± 0.98 versus -1.18 ± 1.14 , $P < 0.05$). In TB-BMD and Ad-SoS, Δ

Table 2 Results of BMD and QUS measurements in all patients and in subgroups without and with GCS use

Group of patients	Mean \pm SD		
	Baseline	Second measurements	Third measurement
<i>All patients n = 18</i>			
Spine BMD (g/cm ²)	0.913 \pm 0.224	0.929 \pm 0.187	0.941 \pm 0.22
Z-score	-1.3 \pm 2.1	-1.43 \pm 1.99	-1.54 \pm 2.31
Total body BMD (g/cm ²)	0.920 \pm 0.125	0.925 \pm 0.120	0.925 \pm 0.121
Z-score	-1.49 \pm 1.5	-1.71 \pm 1.6	-1.87 \pm 1.7*
Ad-SoS (m/s)	1929 \pm 44	1935 \pm 49	1918 \pm 66
Z-score	-2.59 \pm 1.7	-2.67 \pm 1.15	-3.15 \pm 1.2
<i>Patients without GCS use n = 12</i>			
Spine BMD (g/cm ²)	0.924 \pm 0.24	0.954 \pm 0.18	1.006 \pm 0.20
Z-score	-0.76 \pm 1.90	-0.76 \pm 1.65**	-0.54 \pm 1.75***
Total body BMD (g/cm ²)	0.914 \pm 0.12	0.931 \pm 0.11	0.939 \pm 0.11
Z-score	-1.15 \pm 1.18	-1.26 \pm 1.46	-1.31 \pm 1.47
Ad-SoS (m/s)	1919 \pm 45	1927 \pm 45	1923 \pm 50
Z-score	-2.79 \pm 1.89	-2.69 \pm 1.05	-2.78 \pm 0.92
<i>Patients with GCS use n = 6</i>			
Spine BMD (g/cm ²)	0.891 \pm 0.20	0.879 \pm 0.20	0.808 \pm 0.20 +
Z-score	-2.37 \pm 2.23	-2.76 \pm 2.05	-3.45 \pm 2.07 +
Total body BMD (g/cm ²)	0.932 \pm 0.13	0.914 \pm 0.14	0.897 \pm 0.15
Z-score	-2.15 \pm 2.02	-2.6 \pm 1.81	-2.98 \pm 1.84 +
Ad-SoS (m/s)	1949 \pm 38	1950 \pm 57	1913 \pm 91
Z-score	-2.17 \pm 1.43	-2.64 \pm 1.43	-3.9 \pm 1.41 +, + +

*Significant difference versus first measurement, $P < 0.05$

**Significant difference versus adequate value in patients with GCS use, $P < 0.05$

***Significant difference versus adequate value in patients with GCS use, $P < 0.01$

+ Significant difference versus first measurement, $P < 0.05$

+ + Significant difference versus second measurement, $P < 0.05$

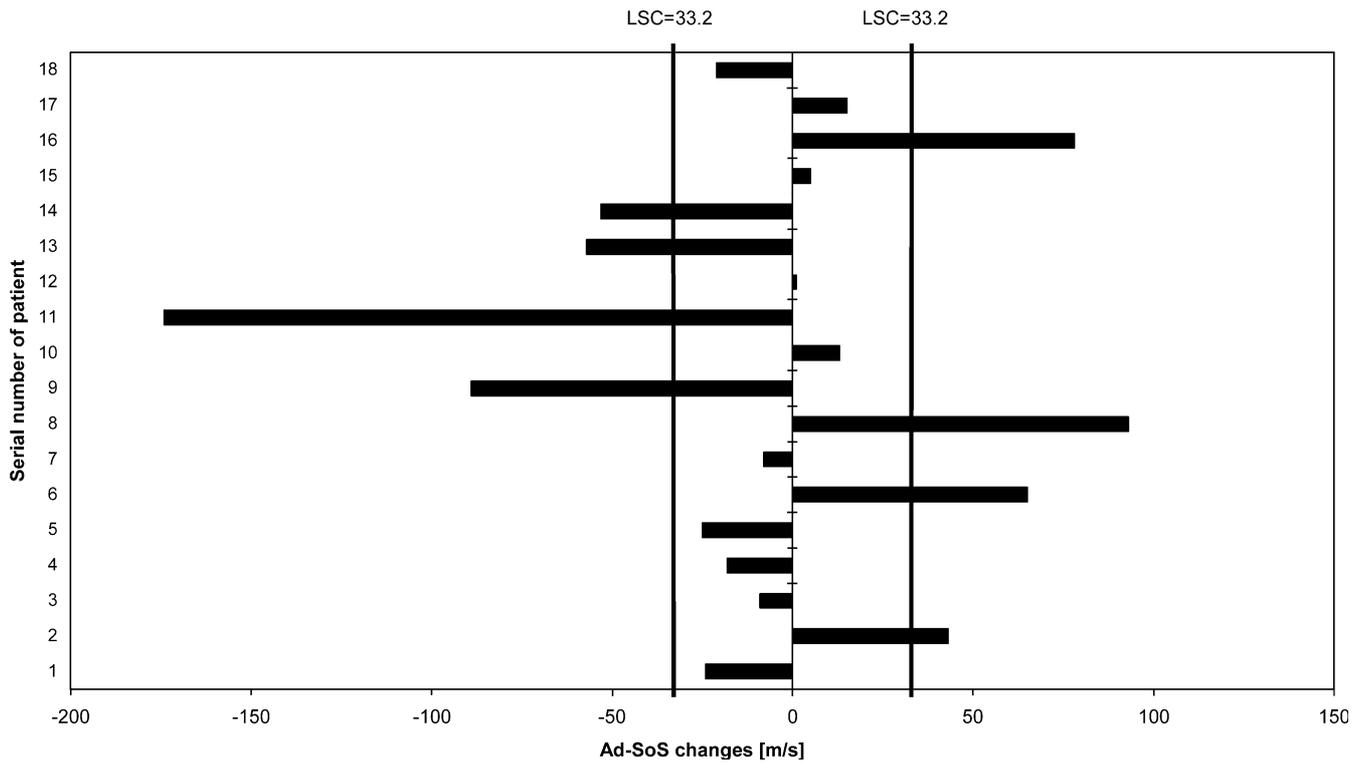


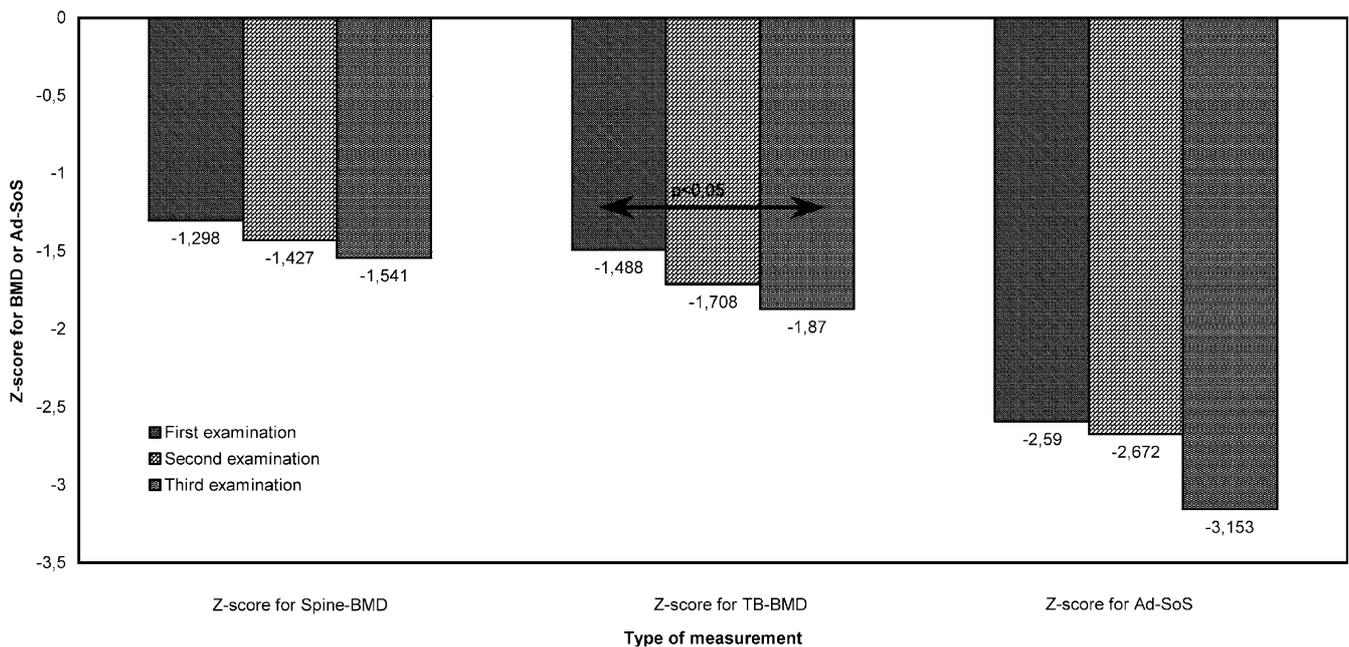
Fig. 1 Changes in Ad-SoS value in individual patients over a period of observation

Z-scores were non-significantly greater in GCS treated subjects, and *P*-values were 0.075 and 0.057, respectively. A comparison of longitudinal values in subgroups showed that several skeletal variables decreased significantly in GCS treated patients, while in patients not taking GCS, decreases were not observed, and s-BMD

even increased significantly between third and first measurement (Table 2).

The change in Z-score for Ad-SoS was not dependent on changes in body size and changes in biochemical parameters, and changes in TB-BMD and s-BMD were dependent on changes in body size and changes in biochemical parameters. In multiple stepwise regression analysis, the following equations were obtained: $\Delta\text{TB-BMD Z-score} = -0.74 + \Delta\text{weight} \times 0.007 + \Delta\text{P} \times 0.73 - \text{ionized Ca} \times 2.5 + \Delta\text{height} \times 0.06$, $r = 0.71$, $P < 0.05$, $\text{SEE} = 0.58$; $\Delta\text{s-BMD Z-score} = -0.89 + \Delta\text{weight} \times$

Fig. 2 Changes in mean value of Z-score for s-BMD, TB-BMD and Ad-SoS over a period of observation



Z-score for Spine-BMD

Z-score for TB-BMD

Z-score for Ad-SoS

Type of measurement

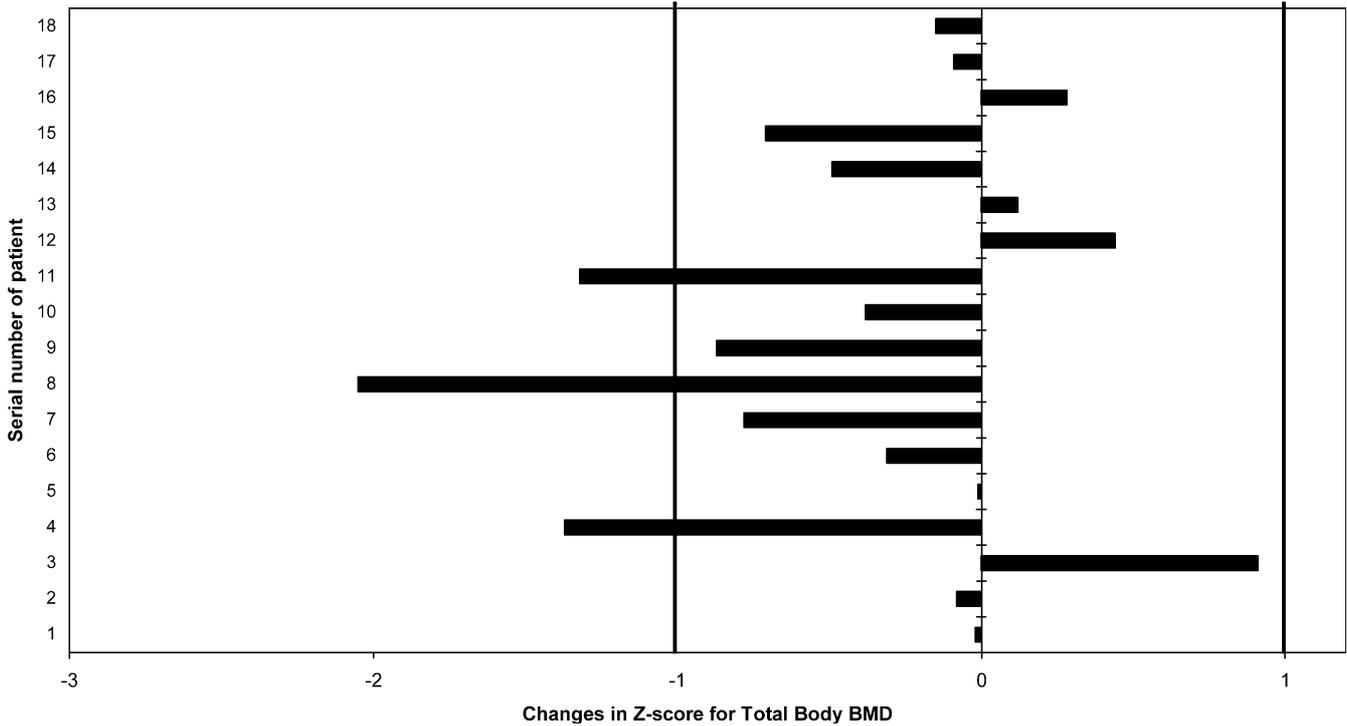


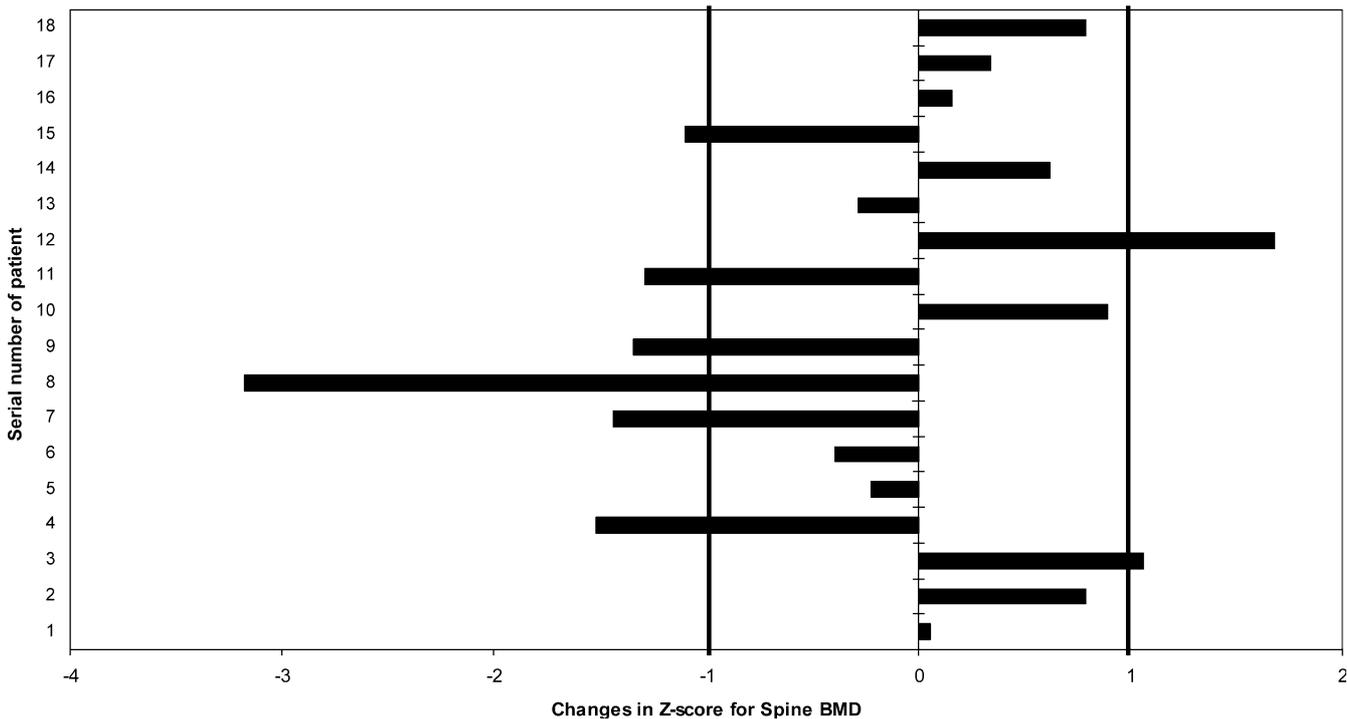
Fig. 3 Changes in value of Z-score for TB-BMD in individual patients over a period of observation

$$0.015 + \Delta P \times 1.14 + \Delta \text{height} \times 0.14 - \Delta \text{ionized Ca} \times 4.41 - \Delta \text{PTH} \times 0.001, r = 0.77, P < 0.05, \text{SEE} = 0.92.$$

Duration of ESRF, duration of dialysis, and sex did not influence skeletal variables (data not shown). Skel-

etal measurements correlated significantly with Tanner stages (besides of correlation with Ad-SoS in first measurement, $r = 0.5-0.72, P < 0.05$), and changes in Tanner stages observed over a period of observation did not correlate with changes in Z-scores for skeletal variables. Among laboratory variables, non-significant tendencies to change were observed: serum concentrations of i-PTH and phosphate increased, and total and ionised calcium decreased. These data are shown in Table 3. Laboratory

Fig. 4 Changes in value of Z-score for s-BMD in individual patients over a period of observation



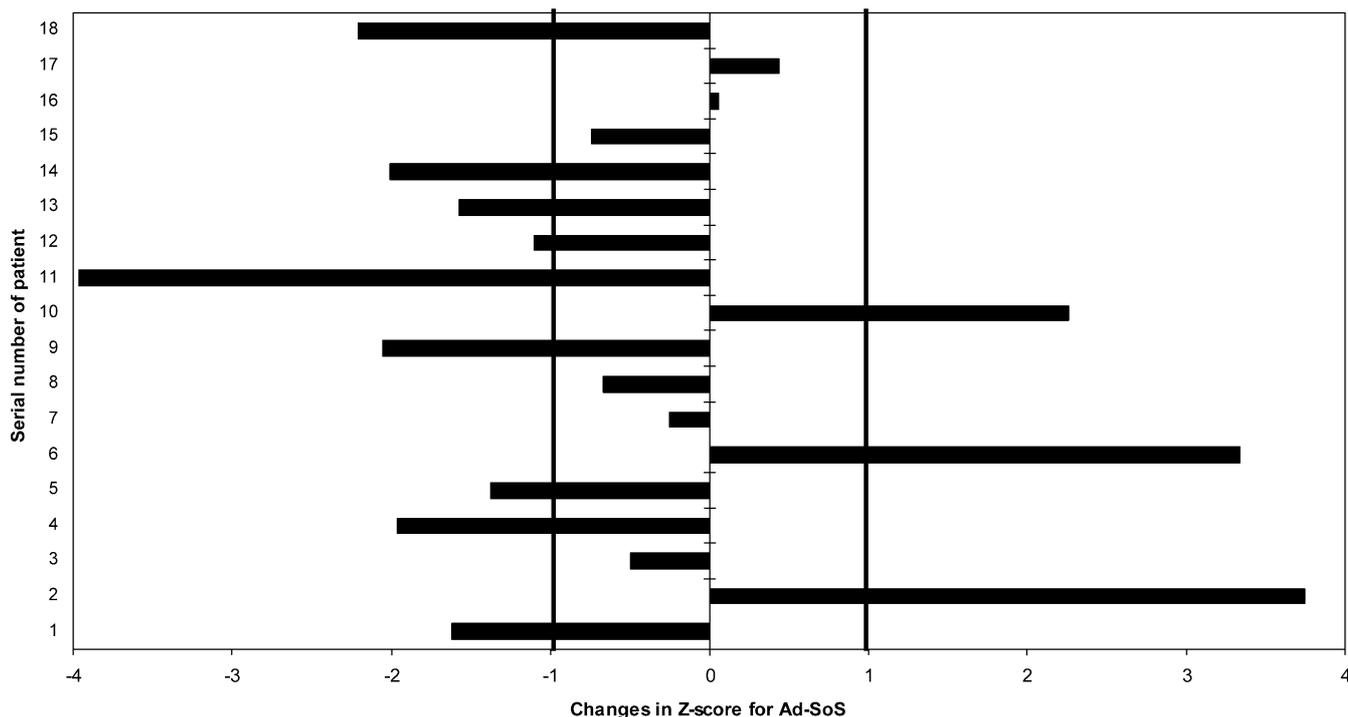


Fig. 5 Changes in value of Z-score for Ad-SoS in individual patients over a period of observation

variables did not correlate with skeletal variables. We also calculated number of subjects with weight and height lower than the third percentile for age and gender. Weight was below this value in all three measurements in nine subjects, and height in first measurement in 11, second in ten and third in nine subjects.

Discussion

The current longitudinal study in adolescent patients with ESRF is a follow-up of our previous cross-sectional study [8]. The skeletal status in the patients studied was seriously affected. To our knowledge, no longitudinal studies on skeletal changes in ESRF in adolescents using QUS and BMD measurements and laboratory investigations have been published so far. The lack of expected increase in densitometric and ultrasound values commonly present in a normal healthy young population, and an obvious parallel decrease in Z-scores, indicate that renal failure caused persistent changes in the skeleton. This observation seems to be the most important finding obtained in the study. Low values of skeletal

variables may be partially attributed to low body weight and short stature in comparison with data from normal age-matched population, and negative Z-scores for body weight and height noted at first measurement even had a tendency to decrease during the study. Another clinically important observation concerns greater skeletal changes in subjects with current or previous GCS use than in the remainder of the patients.

The negative values in Z-score in Ad-SoS and a tendency for Z-score to fall over the time of observation, similar to changes in densitometric variables, indicates that QUS measurements at hand phalanges may be an appropriate method in evaluation of skeletal status in patients with ESRF. The current results confirm observations of earlier, retrospective studies [4,5,7,8,9,10,11,12,13,14,15]. Decreased values in BMD or/and quantitative ultrasound measurements noted by these authors provided information that the skeleton was affected, but in the longitudinal study we were also able to detect changes in the same individuals over a period of almost 2 years. An interesting observation is provided in the recent paper by Groothoff et al. [17]. The authors analysed a group of patients with the onset of renal failure at the age of 0–14 years. Spine BMD measurements performed in 140 subjects at mean age of 29.3 years revealed a mean Z-score value of -2.12 ± 1.4 ,

Table 3 Results of laboratory measurements. Measurements did not differ over a time of observation

	Mean \pm SD		
	Baseline	Second measurements	Third measurement
i-PTH (pg/ml)	321 \pm 281	381 \pm 315	465 \pm 520
Total serum calcium (mmol/l)	2.4 \pm 0.251.14 \pm 0.09	2.4 \pm 0.221.11 \pm 0.14	2.27 \pm 0.211.1 \pm 0.12
Ionized serum calcium (mmol/l)			
Serum phosphate (mmol/l)	1.9 \pm 0.66	1.79 \pm 0.45	1.93 \pm 0.54

which is even worse value than the *Z*-score obtained in our patients (-1.54 ± 2.31). However, a tendency for *Z*-scores to fall, as noted in our group observed over a period of time, indicates that the *Z*-score is likely to reach a similar range in the future. The mean value in *Z*-score for the femoral neck in the same study was -1.77 ± 1.4 , which is very close to our *Z*-score for TB-BMD (-1.87). Some authors have studied longitudinal densitometric changes in patients with chronic renal failure. In a study by Johnson et al. [6] in a small group of children, the value of TB-BMD increased significantly during 6 months of observation, but growth hormone was administered in these patients, so direct comparison is not possible. In an earlier study by Eeckhout [18], a group of 20 adults aged around 55 years who were on regular hemodialysis was evaluated over a period of 3 years. BMC at the spine measured by an older method (dual photon absorptiometry) increased significantly by 8%. Because of different age and different methodology, it is difficult to compare these results with current data. The opposite results were noted in a study published in 1995 by Lyhne et al. [19]. In a study lasting 2 years, forearm bone mineral content decreased by 12% in females (mean age 54 years) but not in males (mean age 60 years). Similar to our analysis, no correlations of serum concentration of i-PTH and skeletal measurement were observed in either longitudinal study in adult populations [18,19]. In our study, we noted a tendency towards an increase in i-PTH and phosphate and a decrease in total and ionized serum calcium; skeletal and laboratory variables did not correlate.

Ad-SoS measured at the hand phalanges consisted mostly of cortical bone [20], and TB-BMD (mainly cortical bone) decreased more than spine BMD (50% of trabecular bone). This result suggests that cortical skeletal sites may be more appropriate in the assessment of bone changes in patients with ESRF. This hypothesis is also supported by the observation of Bianchi et al. [21], who noted a decrease of BMD only in cortical bone. Cortical bone is probably more sensitive to hyperparathyroidism associated with the high level of i-PTH. Our study has some limitations, including small sample size and the lack of data on bone turnover.

In conclusion, adolescent subjects with ESRF treated by dialysis showed stable mean values of skeletal measurements, and if expressed as *Z*-scores, a tendency to decrease was observed. The lack of an increase as observed in normal healthy subjects at the same age, and low values in *Z*-scores, indicates that skeletal status is seriously affected in subjects with ESRF. Further longitudinal observation of subjects studied is in progress.

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