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Vertebral fractures assessment in long-term hemodialysed patients, prevalence and predisposing factors

Renal osteodystrophy (ROD) is a general term for the abnormalities of the skeleton following chronic renal impairment. The first symptoms of ROD can be observed in the early stage of renal insufficiency, when the GFR falls to about 60% of normal. In patients beginning the renal replacement therapy nearly 100% exhibit abnormal bone histology, though they are rarely symptomatic (9,17). ROD can be subdivided into a few groups including: secondary hyperparathyroidism, low turnover osteodystrophy (osteomalacic and adynamic renal bone disease), aluminium toxicity-related osteopathy, mixed uraemic osteodystrophy and β-2-microglobulin bone deposition (7,9). ROD is one of the most important complication impairing the quality of hemodialysis (HD) in patients life, increasing their morbidity and occasionally mortality. Vertebrae fractures (VF) appear to be one of the most hazardous consequences of ROD (4,11). In the general population epidemiological studies have identified several risk factors predisposing to increased bone loss and fracturing bone disease including: advanced age, female gender, loss of gonadal function, decreased physical activity, low calcium intake, alcohol abuse, cigarette smoking, glucocorticoid exposure (12). In HD patients the bone strength can be affected by a number of additional factors. However, only few studies indicate the prevalence of VF in HD patients. Additionally, little information regarding factors predisposing for VF in HD patients has been reported. Moreover, often conflicting data referring to this problem are attainable.

The aim of the study was to evaluate the prevalence of various morphological forms of VF in long-term HD patients, and to analyse the importance of wide range of factors predisposing to VF.

METHODS

Seventy-four HD patients (31 females and 43 males), aged 34–69 years (mean 48.1±10.2), who remained on maintenance haemodialysis from 120 to 297 months (mean 153.4±85.5), were examined. Informed consent was obtained in each case, and the studies were approved by members of the local committees of ethics. The causes of end-stage renal disease were chronic glomerulonephritis (N=41), chronic pyelonephritis (N=10), polycystic kidney disease (N=5), obstructive nephropathy (N=7), and unknown (N=13).

Patients in whom the kidney transplantation was performed as well as HD patients with the history of significant trauma, scoliosis, previously diagnosed or evident Schmorl nodes were not qualified for this study. Those qualified for the study were physically active. Thirty-two HD patients had been submitted to parathyreoidectomy (subtotal in 19 and total in 13). All women were amenorrheic, none had previously taken estrogens. During the study no patients received steroids, anticonvulsant and anticoagulants (except heparin during the dialysis). In addition to

cardiac and antihipertensive therapy, HD patients received sevelamer and/or calcium carbonate. Fifty-eight HD patients had past histories of receiving aluminium gel. Thirty HD patients (40.5%) had previously received corticosteroids for one to eight years before they entered HD treatment. Radiograms that created the control group came from 26 patients (14 female and 12 m ale) of mean age 43.9±11.1 years suffering from sacrodynia after the exclusion of bone course of the disease.

All HD patients underwent lateral radiographs of the thoracic and lumbar spine from Th4 to L5 segments. Anterior, central and posterior heights of vertebral bodies were measured using a digitizer. The number of bicon (BIC), wedged (WED), crushed (CRU) vertebrae were evaluated. Crush fractures were defined by anterior and posterior heights more than 3 SD below the vertebra-specific population mean. Wedge fractures were defined by anterior heights more than 3 SD below the vertebra-specific population mean. Bicon vertebrae were defined by central heights more than 3 SD below the vertebra-specific population mean (13). From the global number of 1,036 studied HD-pts vertebrae, 1,021 could be observed on radiograms and were measurable. In the control group three out of 364 studied vertebrae were not visible or measurable on radiograms.

Aluminium in serum was measured by using electrothermal atomic absorption spectrometry. Mean cumulative $Al(OH)_3$ and steroid doses were calculated on the basis of administrated doses. Mean serum albumin and intact parathormon (PTH) levels as well as mean urea reduction ratio (URR) for entire dialytic period were calculated on the basis of monthly or quarterly biochemical examination results starting from the three month after the beginning of the HD treatment.

Statistical analysis was carried out on an IBM PC using Statistica Version 5. Linear regression analysis was performed by using the two-tailed Pearson test. Multiple stepwise regression analysis was performed to estimate the potential influence of various factors on WED, BIC and CRU vertebrae. Probability values of less than 0.05 were accepted as significant.

RESULTS

Table 1. Results of radiological survey, and biochemical parameters in patients and in controls

	Hemodialysed patients	Control group	
Parameter	mean ± SD	mean ± SD	p
WED (n =28)	0.333 ± 0.406	0	p<0.001
BIC (n=20)	0.238 ± 0.437	0	p<0.001
CRU (n=18)	0.214 ± 0.347	0	p<0.001

Results of spine deformities assessment in HD patients are shown in Table 1 and Figure 1. Twenty nine-HD patients (39.2%) revealed the presence of spine deformities. The most frequently occurring morphological forms of spine deformities were WED, next BIC, and CRU vertebrae.

Twenty HD patients (27.0%) had fractured (WED or CRU) at least one spine segment, 12 (16.2%) of them had multiple fractures. Out of eight HD patients who revealed BIC vertebrae, six had multiple deformations. Only one HD patient had both BIC and fractured vertebrae. When data were expressed as a number of VF per year of dialysis, the ratio was: 0.0315 for WED, 0.0228 for BIC, and 0.0206 for CRU. Most of all morphological forms of SpD were localized in two regions. The first region were segments Th_{10}–L_1 (50.7% of all SpD) and the second was segment L_5 (14.5% of all SpD). The relation between WED and CRU was significant ($r = 0.561$, $p<0.01$), but the relations between BIC and WED or BIC and CRU were not significant. In the control group we found no radiological evidence of SpD according to our criteria (Table 1). Mean serum aluminium level was 29.79±19.49 μg/l. In eight HD patients serum aluminium levels were above 50 μg/l. BIC deformities were observed only in HD patients with aluminium level exceeding

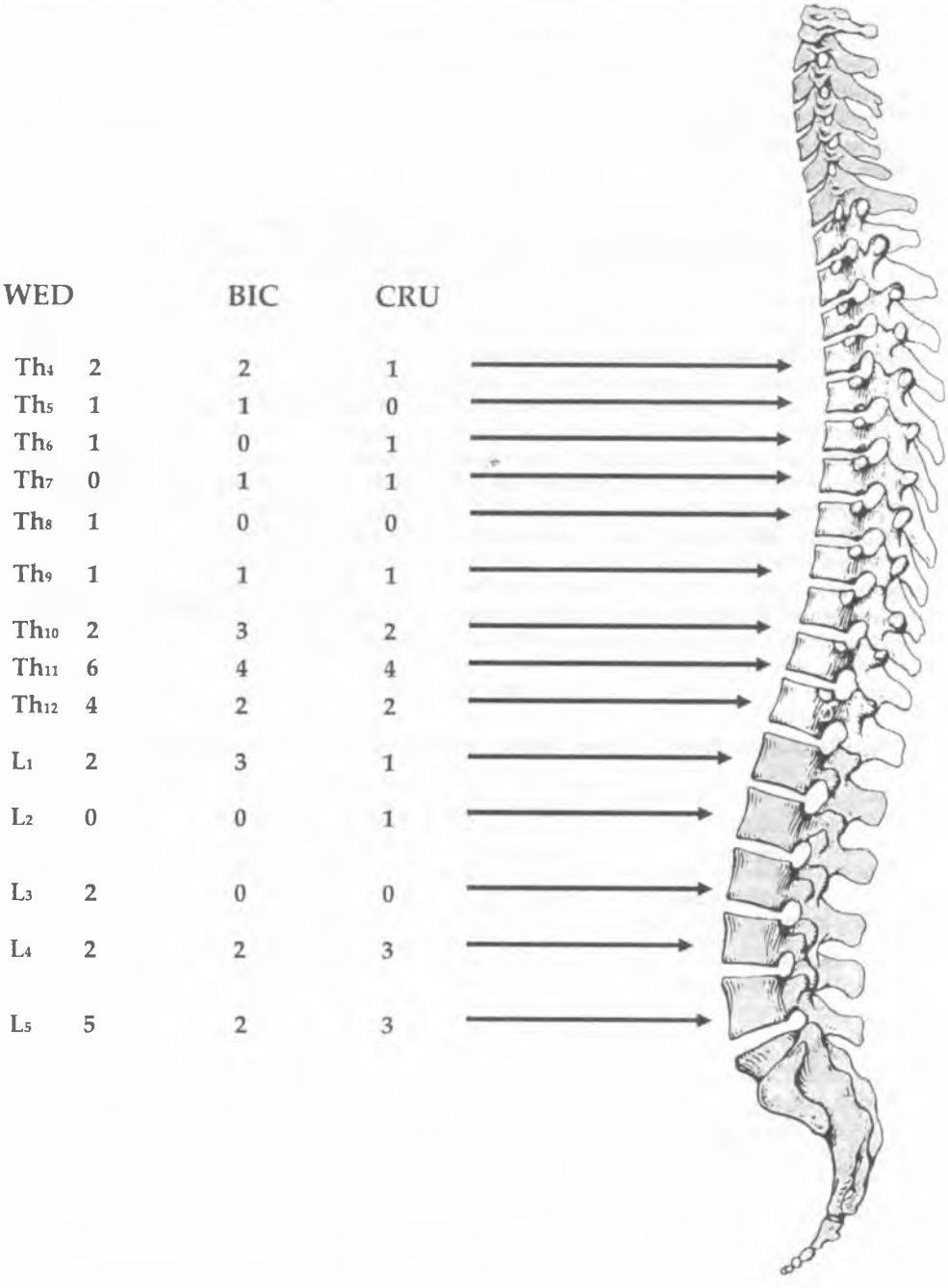

Fig. 1. Results of radiological survey in hemodialysed patients

50 μg/l. BIC as the only morphological type of SpD was positively correlated to serum aluminium level (r=0.316, p=0.004).

Table 2. Patient characteristics

Characteristic	Value (mean±SD)	Range
Age	48.1±10.2	34–64
Time on hemodialysis (months)	153.4±85.5	120–297
Mean albumin for entire dialytic period (g/dl)	3.53±1.37	2.3–4.7
Mean PTH for entire dialytic period (ng/l)	280.1±198.4	12–1132
Mean URR for entire dialytic period (%)	65.1±10.1	43.0–83.2
Cumulative steroid dose (mg)	8606±12757	0–71887
Cumulative $Al(OH)_3$ dose (g)	6390±7112	0–18176

Table 3. Independent variables reaching significance from stepwise multiple regression analyses using the number of wedged, crushed, and bicon vertebrae as dependent variables

	Independent variables	B	Statistic error	Beta	p
Wedged vertebrae	HD duration	3.86	1.34	0.561	<0.001
	mean PTH < 150 pg/ml	- 4.29	1.82	- 0.547	<0.001
	mean albumin	- 27.7	7.23	- 0.409	0.018
	cumulative steroid dose	92.7	33.2	0.399	0.020
	mean PTH > 300 pg/ml	6.18	2.87	0.389	0.031
	$R^2 = 0.640$				
Crushed vertebrae	HD duration	4.59	1.97	0.534	<0.001
	mean PTH < 150 pg/ml	- 5.02	2.02	- 0.530	<0.001
	cumulative steroid dose	28.5	8.92	0.528	<0.001
	mean albumin	- 9.51	4.99	- 0.519	0.004
	mean PTH > 300 pg/ml	21.4	11.4	0.509	0.011
	$R^2 = 0.598$				
Bicon vertebrae	HD duration	4.51	1.08	0.653	<0.001
	cumulative $Al(OH)_3$ dose	15.5	4.991	0.639	<0.001
	mean PTH < 150 pg/ml	- 5.18	2.04	- 0.427	0.016
	$R^2 = 0.671$				

Possible risk factors for various morphological form of VF (WED, CRU and BIC vertebrae) were entered as independence variables in a stepwise linear multiple regression analysis. These included all the factors listed in Table 2 and, in addition, gender of HD patients. The results of multiple regression analysis showing independent variables influencing the estimated morphological forms of VF are depicted in Table 3. In the case of WED and CRU vertebrae the following independence predictors were found: (1) HD treatment duration; (2) mean serum albumin for entire dialytic period; (3) cumulative steroid dose; (4) low (<150 pg/ml) and high (>300 pg/ml) mean PTH for entire dialytic period. The independence predictors of BIC vertebrae were: (1) HD treatment duration; (2) cumulative $Al(OH)_3$ dose and; (3) low (<150 pg/ml) mean PTH for entire dialytic period.

DISCUSSION

Our study revealed high prevalence of VF in HD patients. However, it is difficult to compare our results to the attainable data on skeletal surveys in HD patients, because there are only few studies concerning the HD patients' spinal fractures in the literature. Moreover, most of them do

not distinguish between vertebral and nonvertebral fractures (2, 11), and provide no data about the age of patients and duration of HD treatment (2). In the recent study of Atsumi et al. (1), the authors estimated that the prevalence rate of VF in a group of HD patients males was as high as 21%. Available reports estimate the prevalence of spontaneous fractures in HD patients (vertebral and nonvertebral) from 0 to 37% (1,2,10), and abnormal radiograms of the spine in approximately 61% of HD patients (10). When our data were expressed as "fractures per dialysis year ratio" it turned out that our results were very similar to those obtained by Piraino (11). The discrepancy in VF prevalence in various studies suggests that there may be differences in geographic ROD expression, in the techniques used to detect bone disease and differences due to duration of treatment, race, the age of HD patients and type of predominately bone changes. We observed that most of all morphological forms of SpD were localized in the region from Th10 to L1 as well as in segment L5. It is in agreement with localisation of VF in osteoporosis, as well as biomechanics of vertebral column (12). When we analysed (multiple regression analysis) the association of VF with biochemical and demographic parameters, it turned out that HD duration, average albumin ad PTH levels from the entire dialytic period and previous steroid treatment are independence factors of VF. Surprisingly, we observed differences between factors predisposing to WED or CRU and BIC vertebrae.

The only factor that negatively influenced all morphological VF was the duration of HD treatment. It follows the conclusion of most authors (1,10,11,17). Others, however, contest this view (6, 16). The lack of correlations between HD duration and intensity of ROD findings may result from the fact that in both cited papers the authors estimated patients with dialysis time shorter more than twice than in our study.

Aluminium intoxication is known to affect bone status in HD patients. The investigated patients were dialysed for a long time and were moderately aluminium intoxicated. In our study total aluminium hydroxide intake was the independence factor of BIC vertebrae. It confirms previous observations (2,4,50) that aluminium intoxication influences bone status, predispose to VF, and remains to be a problem in long term HD patients. Taking into consideration that BIC were observed only in HD patients with serum aluminium level exceeding 50 μg/l, and showed significant correlations with not only cumulative $Al(OH)_3$ intake but also baseline serum aluminium level, this morphological form of VF seems to be especially associated with aluminium intoxication, but the reason of this phenomenon is not clear.

Our study revealed that chronic hypoalbuminemia might play a role in the pathogenesis of VF, especially WED and CRU vertebrae. The finding of a negative association of chronic hypoalbuminemia and VF in HD patients was unexpected and, as far as we are informed, has not been reported previously. The only attainable study of Eisenberg (3) indicated hypoalbuminemia as a factor affecting bone mineral density of HD patients' femoral necks but not lumbar vertebrae. Data referring to the role of protein deficiency in the pathogenesis of osteoporosis is conflicting. In several clinical studies authors have observed positive, negative relationships or no association between protein intake and osteoporosis (12). Prolonged deficiency of protein may probably lead to quantitative or/and qualitative disorders of organic phase synthesis and the defect of bone structure. However, the reason why such a defect is especially connected with the occurrence of WED and CRU needs further investigation.

Corticosteroids affect especially axial bone and VF are well documented complications of long-term steroid therapy (14). Taal et al. (16) have found no association between cumulative steroids dose and bone mineral density in HD patients. It may result from the fact that in our study the leading course of the end stage renal disease were glomerulonephritis, and the average cumulative steroid dose was nearly twice as high as in Taal study.

It is generally accepted that PTH levels below 100 pg/ml are associated with an increased incidence of adynamic bone disease, whereas levels above 450 pg/ml point to *osteitis fibrosa cystica*. Both types of ROD are associated with increased fracure risk in HD patients (9, 17), however, low turnover ROD is associated with higher fracture rate than hyperparathyroidism, especially when referring to axial skeleton (11, 14). Our study confirms most of the previous observations that both low and high levels of PTH are associated with increased fracture risk

(11, 17), though some authors have not found such a relation (1, 16). We belive that our study provides additional data supporting the use of target PTH levels between 150 and 250 pg/ml as a strategy to preseve skeletal health, and to prevent VF in HD patients.

The age-dependent bone loss is a universal process. It plays an important role in the pathogenesis of osteoporosis in normal adults at a rate of 1–2% per year over the age of 40 years, increasing to 2–4% following menopause (15,16). The lack of correlations between age and radiological findings in our study may probably result from the fact that authors who have found relations between the age of HD patients and intensity of ROD findings (6,11,16) estimated approximately twice shorter dialysis patients.

CONCLUSIONS

Our study revealed high prevalence of VF in long-term HD patients. We have confirmed the importance of some factors predisposing to VF (duration of HD treatment, both high and low PTH levels, aluminium exposure, previous steroid therapy). Our study revealed that chronic hypoalbuminemia might play an important role in the pathogenesis VF. Our study supports that the maintenance of intact PTH level between 150–300 pg/ml is associated with lower VF risk in HD patients.

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SUMMARY

The study was to evaluate the prevalence of vertebral fractures (VF), and to estimate factors predisposing to VF in long-term (over 10 years) hemodialysis (HD) patients. On the basis of radiographs from Th_4 to L_5 the number of wedged, crushed, and bicon vertebrae were evaluated in 74 patients and in controls. Mean cumulative $Al(OH)_3$ and steroid doses were calculated in patients. Mean serum albumin and intact parathormon (PTH) levels for entire dialytic period were calculated. Spine deformities were found in 39.2% of patients (wedged or crushed vertebrae were found in 27.0%, bicon vertebrae in 10.8% of patients). Multiple fractures were found in 16.2% of patients. Multiple regression analysis revealed the following independence predictors of wedged and crushed vertebrae: (1) HD treatment duration; (2) low mean albumin for entire dialytic period; (3) cumulative steroid dose and; (4) low (<150 pg/ml) and high (>300 pg/ml) mean PTH for entire dialytic period. The independence predictors of bicon vertebrae were: (1) HD treatment duration; (2) cumulative $Al(OH)_3$ dose and; (3) low (<150 pg/ml) mean PTH for entire dialytic period. Conclusions: In long-term HD patients the prevalence of VF is high. We have confirmed the importance of some kown factors predisposing to VF, and revealed that chronic hypoalbuminemia might play an important role in the pathogenesis of VF. Our study confirms that the maintenance of intact PTH level between 150–300 pg/ml is associated with lower risk VF in HD patients.

Złamania kręgosłupa u długo hemodializowanych pacjentów: częstość występowania, czynniki usposabiające

Celem pracy była ocena częstości występowania oraz zdefiniowanie czynników predysponujących do złamań kręgosłupa (ZK) w grupie długo (powyżej 10 lat) hemodializowanych pacjentów. Na podstawie zdjęć radiologicznych odcinka Th_4-L_5 kręgosłupa określono w grupie 74 pacjentów oraz w grupie kontrolnej liczbę kręgów złamanych klinowo, kompresyjnie oraz dwuwklęsłych. Obliczono średnie kumulacyjne dawki $Al(OH)_3$ oraz sterydów, przyjęte przez pacjentów, jak również średnie (z całego okresu dializoterapii) stężenia albuminy i intact parathormonu (PTH). Deformacje kręgosłupa stwierdzono u 39,2% pacjentów (złamania klinowe oraz kompresyjne u 27%, natomiast kręgi dwuwklęsłe u 10,8% pacjentów). Mnogie złamania występowały u 16,2% chorych. Na podstawie wyników regresji wielokrotnej wykazano następujące niezależne czynniki predykcyjne złamań klinowych i kompresyjnych kręgosłupa: (1) czas dializoterapii; (2) niskie średnie stężenie albuminy; (3) kumulacyjna dawkę steroidów oraz (4) niskie (<150 pg/ml) i wysokie (>300 pg/ml) stężenie PTH. Niezależnymi czynnikami predykcyjnymi występowania kręgów dwuwklęsłych był: (1) czas dializoterapii; (2) kumulacyjna dawka $Al(OH)_3$; (3) niskie (<150 pg/ml) stężenie PTH. Wnioski: Częstość występowania ZK wśród długo hemodializowanych pacjentów jest wysoka. Potwierdzono znaczenie niektórych znanych czynników predysponujących do złamań kręgosłupa oraz wykazano, iż przewlekła hipoalbuminemia może odgrywać istotną rolę w patogenezie ZK. Wyniki pracy potwierdzają, że utrzymywanie stężenia PTH w granicach 150–300 pg/ml związane jest z mniejszym ryzykiem występowania ZK.