Frequency of Metabolic Bone Disease in Haemodialysis Patients

Pages with reference to book, From 83 To 86

Rizwan Hussain, Arshad Ahmed, Abdul Salam Soomro, Saeed Hassan Chishty, Syed Ali Jaffar Naqvi (The Kidney Centre, Sarfaraz Rafiqui Shaheed Road, Karachi.)

Abstract

The frequency of metabolic bone disease related to secondary hyperparathyroidism was studied in 47 haemodialysis patients, using biochemical, radiological parameters and bone biopsy (30 males, 17 females; mean age 48 years). The duration on dialysis ranged from 1-5 years. Hypocalcemia was found in 47% while 62% had raised phosphorus levels and 49% raised alkaline phosphatase. Serum parathyroid hormone was elevated in 86%, while in 13% it was markedly raised. On radiological examination there was generalized osteopenia in 49% and decreased bone density in 21%. In 30% no radiological abnormality was detected, In 40% bone biopsy revealed osteomalacia, mixed osteodystrophy 21%, osteoporosis 8.5% and in 25% no histological abnormality was observed (JPMA 46:83, 1996).

Introduction

Secondary hyperparathyroidism develops in most patients with End Stage renal disease (ESRD) and may cause severe metabolic bone disease and extrosseous calcification. The main factors leading to the excess parathormone (PTH) and parathyroid hypeiplasia are phosphate retention and reduced gastro intestinal absorption of calcium due to reduced synthesis of 1,25 dihydroxy vitamin D3 (1,25 (OH)2 D3). Compounding factors are end organs (bone) resistance to parathyroid hormone, few parathyroid receptors for 1,25 $(OH)_1$ D3. impaired degradation of PTH secondary to reduced renal function and alteration in glandular response to serum calcium level[1].

Differences in PTH level have been noted in maintenance haemodialysis patients with different forms of renal osteodystrophy. The predominant bone disease in dialysis patients has been osteitis fibrosa characterized by an increase in osteoblast surface, bone resorption and the bone formation rate[2-7]. However during the late l970s and early in 1980s, a significant number of patients were found to have low-turn- over aluminium related bone disease (LTARBD) which was associated with a relative deficiency of PTH, a decrease in osteoblast surface, the presence of stainable bone aluminium, osteoid accumulation, and decreased rate of bone formation[8-11]. Recently an increased number of dialysis patients with aplastic bone disease also called as “adynaniic bone disease” has been reported[12,13]. These patients also have relative PTh deficiency and similar bone histology as patients with LTARBD except that stainable bone aluminium is absent and osteoid accumulation is not observed[13]. The aim of the present study was to determine the frequency, types and severity of bone disease in patients on maintenance haemodialysis.

Patients and Methods

Forty-seven patients of ESRD on maintenance haemodialysis at the Kidney Centre for more than one year duration were studied. These patients were on acetate haemodialysis with the duration of four hours twice weekly. Treated water (reverse Osmosis) was used in dialysis. Almost all the patients were on phosphate binders (Calcium Carbon¬ate, dose ranged from 1.5 to 3.0 G/day) but not on vitamin D preparation. Serum aluminium levels were not measured due to non-availability of this test when the

study was performed. Patients with bone tuberculosis, malignancy, rejected trans¬plant and rheumatoid arthritis were excluded from the study. Metabolic bone parameters (calcium, inorganic phosphorus. alkaline phosphatase) were evaluated by micro-lab analyzer. Mid molecularparathormone level was estimated by radioim¬munoassay. In skeletal survey, x-ray both hands and pelvis, were carried out and bone density was assessed subjectively[14]. Osteopenia revealed thinning of bone cortex and rarification, while decreased bone density means lesser thinning of bone cortex as compared to osteopenia. Non-decalcified trephine bone biopsy was performed and stained with haemotoxylin, eosin (H&E) and vonkossa stain and not for aluminum due to lack of facility. Patient clinical data from medical record was also obtained.

Results

Thirty males and 17 females (mean age 48 years) were studied. The cause of ESRD was chronic glomerulonephritis in 33%, diabetes mellitus in 21%, hypertension in 19%, adult polycystic kidney disease in 14% and chronic pyelonephritis in 12%. Seventeen cases were on dialysis since 1-3 years, 14 since 2-3 years, 13 since 3-4 years and 3 for more than 5 years. Poor compliance to diet was present in 21%, 6%to medication and 4% to dialysis. Results of different metabolic bone parameters are shown in Table I.

Table I. Values of metabolic bone parameters.

Parameters		Normal	Low	High
Serum calcium	No	24 (51%)	22 (47%)	1
(mg/dl)	Range	8.6-10.5	7-8.5	11.2
	Mean±SD	9.4±0.48	8.1±0.46	
Inorganic	No	17 (36%)	1	29 (62%)
Phosphorus	Range	2.8-4.9	2.5	5-11.9
(mg/dl)	Mean±SD	3.9±0.68		6.8±1.73
Alkaline	No	24 (51%)	#	23 (49%)
Phosphatase	Range	86-291		305-3035
(U/L)	Mean±SD	182±55		681±571
Parathyroid	No	1	#	46 (98%)
Hormone	Range	0.12		0.69-16.4
(ng/ml)	Mean±SD			3.91±3.04

Hypocalcemia was present in 47% while 62% had raised phosphorus. 49% raised alkaline phosphatase and 86% raised parathyroid honnone. On radiology 30% had no radiological abnormality, decreased bone density was present in 21% and osteopenia in 49%. Bone biopsy revealed osteornalacia in 40% characterized by bone trabeculac with wide non mineralized osteoid alongwith osteoblastic lining. There was no marrow fibrosis and osteoblastic activity was not increased. The second common

pathological lesion was mixed osteodystrophy (Osteitis fibrosa and osteomalacia) in 21% which was associated with non- mineralized pink osteoid. There was prominent osteoblastic and osteoclastic activity with increase in marrow fibrosis. Osteoporosis was reported in 8.5%. Histologically bone trabeculac were widely separated from each other and lined by fatty marrow. In 25% no histological abnormality was detected.

Bone biopsy was not possible in 4% because of obesity and severe bone pain. Pattern of metabolic bone disease and its relation with biochemical and radiological parameters are given in Table II.

Table II. Pattern of metabolic bone disease with biochemical and radiological features.

Bone biopsy Histological lesion	Hypocalcemia <8.6 mg/dl	Raised phosphorus >5 mg/dl	Raised Alkaline Phosphatase 400-3335 U/L	Osteopenia	Decreased Bone dens	Elevated Path
Osteomalacia 40%	68%	63%	63%	68%	32%	Mild to mod=89%, Marked Elevated=11%.
Mixed osteodystrophy (Osteitis Fibrosa) Ostemoazacia 21%	50%	80%	90%	70%	30%	Markedly elevated 30%
Osteoporosis 8.5%	Normal CA	Normal IP	Normal Alk. Pho	Nil	75%	Mildly elevated 98%
Normal 25%	Nil	33%	Nil	Nil	Nil	Mildly elevated 83%

Biopsy not possible in 4% due to obesity and pain
Osteopenia: Thining of bone cortex and rarefaction in bones
Decreased bone density: Lesser thining of bone cortex as compared to osteopenia.
Elevated PTH: Mildly eleated (Upto 3.0 ng/ml)
Moderately elevated (3.0-7.0 ng/ml)
Markedly elevated (Upto 16.0 ng/ml)
Statistically P= Non significant.

Osteopenia was found in 21% while decreased bone density was found in 49%.

It was noticed that the presence of renal bone disease in relation to etiology of ESRD was 100% in chronic pvelonephritis, in diabetes 60% and polycystic kidneys 50%. We also observed the effect of duration on dialysis on renal bone disease, 3 patients who were on dialysis for more than 5 ears had 100%prcsenceof disease and it was 59% in 17 cases who were on dialysis since 1-2 years.

Discussion

The results of this study represent osteomalacia as a dominant renal bone disease.It can be due to dietary deficiency of vitamin D3 or decreased endogenous synthesis of vitamin D3 or due to aluminum intoxication. This is unlikely to be due to aluminum intoxication because aluminum free reverse osmosis treated water was used for dialysis and also the calcium compound phosphate binders instead of aluminum containing compounds were used. Regarding osteoporosis, 3 of 4 patients were females, aged more than 55 years, so estrogen related osteoporosis cannot be ruled out.

Our result are different from other studies conducted abroad'5. The possible reason could be that investigations carried out in our set up were i) albumin related total serum calcium level ii) mid molecular parathormone and iii) subjective assessment of bone density, The bone biopsy was only seen with H&E stain and vonkossa stain. The assessment of ionized calcium, intact parathormone, vitamin D3, bone mineral density by dual x-ray absorptiometry (DEXA), serum aluminum, bone biopsy with tetracycline labelling and for stainable alurninumwere not available inour set-up while they are frequently done abroad[14-16]. This was our pilot study but in subsequent studies, we will be able to perform bone biopsy with tetracycline labelling and for stainable aluminum.

Studies from 1970s through mid 1980s have indicated that the most common form of renal osteodystrophy is osteitis fibrosa[3]. This is characterized by very high parathormonc level[7]. Although not fully confirmed there has been some recent suggestions that the frequency ofosteitis fibrosa may be decreasing. This may be due to factors which decrease PTFI, e.g.. the more liberal use of vitamin D3. the use of calcium compounds as phosphate binders and also greater number of diabetics as dialysis patients. In our study we did not observe osteitis fibrosa but mixed osteodystrophy (osteitis fibrosa and osteonialacia) was common.

We also noticed that patients with diabetes mellitus have mildly elevated PTH (upto 3.0 ng/ml) and lower prevalence of bone disease as compared to non diabetics[17]. But this was statistically not, significant. The mean survival in diabetic patients on hemodialysis at our Centre is almost 2 years. This may be the possibility showing low prevalence of bone disease inthis group. We confirmed the results of Briger et al.. the renal osteodystrophv was significantly raised as duration on dialysis increases[18].

We conclude that frequency of metabolic bone disease in our dialysis patients is 70%. The commonest pathological lesion is osteomalacia (40%). followed by mixed osteody strophy (2 1%) and osteoporosis (8.5%). Further studies arc needed to determine the therapeutic measures for prevention of renal osteody strophy.

References

1. Melan, A., Schittl, H., Held, E. et al Assessment of acute parathyroid responsiveness to high calcium dialysate in uremic patient. Int. J. Artif. Organs. 1993;16:711-15.
2. Hruska. K.A., Teitelbaum, S.L., Kopleman, R. et al. The predictability of the histological features ofuremic bone disease by non-invasive techniques. Metab. Bone Dis Re!. Res., 1978:1:39-44.
3. sherrard, D.J Baylink. D.J., Wcrgcdal, I.E. et al, Quantitative histological studies in pathogenesis of uremic bone discase, J Clin. Endocrinol. Metab,. 1974;39:119-135.
4. Clian, Y.L., Furlong, TJ., Comish, C.J. et al. Dialysis osteodystrophy A study involving 94 patients. Medicine, 1985;64;296-309
5. Ritz,E., Prager,P., Krempien, B. etal. Skeletal x-ray findings and bone histology in petients on haemodialysis. Kidncy. Int., 1978;13:316-323
6. Alvarez V.F Feest, TO., Wards, M.K et al Haemodialysis bone disease. Correlations between clinical, histologic and other findings. Kidney. Int.,15:78;14:68-73.
7. Llach, F., Felsenfeld, A.J., Coleman, MD. ct al. The natural course of dialysis ostcomalacia Kidney Int., 1 986;29 (Suppl 18): 574-979.
8. Andress D., Felsenteld, A. J., Voigts, A. et al. Parathyroid hormone response to hypocalcemia in haemodialysis patients with osteomalacia. Kidney Int., 1983;24:364-370.
9. Parkinson, I.S., Feest, Ti.. Ward. M,K etal. Fracturing dialysis osteodystrophy and dialysis encephalopathy: An epidemiological survey. Lancet, 1979:1:406-409.
10. Ott, SM., Maloney, NA., Cohurn. J W, et al. The revelance ofbone aluminium deposition in renal osteodystrophy and its relation to the response to calcitriol. N. Eng. J. Med.. 1982;307:709-713.
11. Hodsman, A.B Sherrard, D.J., Wong. EGG. et al. Vitamin D resistant osteomalacia in haemodialysis patients lacking secondary hyperparathyroidism. Ann, Intern Med.. 1981;94:629-637. 637.
12. Andess, D.J.., Endres, D.B., Maloney, NA, et al. Comparison of parathyroid hormone assay wth bone histomorphometrv in renal osteodystrophy J. Glin. Endoerinol. Metab., 1 986;63: 1163-69.
13. European PTH Study Group. Interlahoratory comparison of radioimmunologicat parathyroid hormone determination. Eur. J. Clin. Invest., 1978;8: 149-154.
14. Badani, P.L., Orzincolo. C., Storari, A. et all. Clinical and radiological featuresof bone disease in long term (15 or more years) haemodialysis patients. Int. J. Artil Organs, 1993;16(10):704-710.
15. Hutenison, AJ., Whitehouse, KW., J3outton, HF. et al. Correlation of bone histology with

parathyroid hormone, vitamin D3 and radiology in End Stage Renal Disease. Kidney Int., 1993;44(5):1071-1077.
16. Zhu, P., Wang, G,Y., Yu, Y.F. et al. Aluminium in renal osteodystrophy. Chung Hua. Nei. Ko. Tsa. Chih., 1993; 32(3); 176-78.
17. Cundy, TV, Humphreys. S. Watkins, P.J. et al. Hyperparathyroid bone disease in diabetic renal failure. Diabetes. Res., 1990; 14(4): 191-196.
18. Briger, L., Olef, J. Nilsson, BE. et al. Studies of bone morphology, Bone densitometry and laboratory data in patients on maintenance haemodialysis treatment, Nephron., 1985 ;39: 122-129.