THE SPECTRUM OF RENAL OSTEODYSTROPHY IN CHILDREN ON CONTINUOUS AMBULATORY PERITONEAL DIALYSIS

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SUMMARY :

Purpose : *The prevalence of different types of bone disease in chronic renal failure (CRF) has changed significantly during the last decade. The aim of this study is to evaluate the spectrum of bone disease in children with CRF undergoing continuous ambulatory peritoneal dialysis (CAPD).* ***Methods :*** *Seventeen children with CRF on CAPD aged 7 to 20 years were evaluated. All patients had received regular vitamin D and calcium carbonate therapy during the six months preceding the bone biopsy. Serum calcium, phosphate, alkaline phosphatase and intact parathyroid hormone (iPTH) levels were measured and hand X-rays were performed. Transiliac bone biopsies were analyzed for histological diagnosis.* ***Results :*** *High turnover renal osteodystrophy (ROD) was the most common bone disease, present in 8 (48%) patients. Five (29%) patients had adynamic bone disease, and 4 (24%) had mixed ROD. The mean age of high turnover ROD group was higher than the adynamic group (14±3 vs 11±3 years, $p<0.05$). Seven of the 9 patients who had tubulo-interstitial nephritis were found to have high turnover (HTO) bone disease . On the other hand none of the patients with glomerulonephritis exhibited HTO bone lesion . Mean serum calcium levels were significantly higher in the low turnover (LTO) group when compared to the patients with HTO bone disease ($p<0.001$). A serum iPTH level >200 pg/ml was 100% sensitive and 66% specific in identifying patients with high turnover ROD.* ***Conclusion :*** *The spectrum of bone disease of children with CRF undergoing CAPD seems to depend on the rate of CRF and primary disease. The risk of developing overt hyperparathyroid bone disease is seen in children with slowly progressing forms of renal pathology and especially those with tubulo-interstitial disease. On the other hand, children with glomerular diseases who had a more rapidly progressive course may have a lower risk of developing high turnover bone disease. The results of the present study indicate that even routinely prescribed regular vitamin D therapy early in the course of the disease may lead to LTO bone lesion in small children who had CRF, due to rapidly progressive forms of renal pathology.*

Key Words: *Renal Osteodystrophy, Child, Continuous Ambulatory Peritoneal Dialysis.*

INTRODUCTION

The pathogenesis of renal bone disease in chronic renal failure (CRF) is complex and includes alterations in the metabolism of calcium, phosphorus and vitamin D, disturbances in the secretion and regulation of parathyroid hormone (PTH), and impairments in the regulation of acid-base homeostasis. Most of the cases show

histological evidence of high turnover (HTO) bone disease despite ongoing treatment with oral calcitriol (1). However, the spectrum of bone disease in CRF has changed significantly during last decade (2,3). The incidence of low turnover (LTO) bone disease without aluminum toxicity has been increasing in the pediatric population (4). However, there is limited information about the frequency of various histologic subtypes of renal bone disease and their progression in patients undergoing continuous ambulatory peritoneal dialysis (CAPD), particularly in children.

The aim of the present study is to evaluate the spectrum of bone disease in children with CRF and undergoing CAPD.

PATIENTS AND METHODS

Seventeen patients (8 males, 9 females) with CRF, aged 7-20 years (mean: 13.0±3.0 years) who had been clinically stable on CAPD for at least six months, were enrolled in this cross sectional study. None of the patients had been on a hemodialysis programme. Informed consent was obtained from the patients and/or their parents. The study was approved by the ethic committee. Primary renal diseases were chronic tubulo-interstitial nephritis (9 patients), glomerulonephritis (4 patients), cystinosis (2 patients), Alport syndrome (1 patient), and juvenile nephronophthisis (1 patient). Standard CAPD fluids that include 1.75 mmol/l calcium were used unchanged during the study, exchanging 30-50ml/kg of 1.36% and/or 2.27% dextrose solution four times daily. The duration of follow up as CRF and on CAPD were 6-120 months (mean 42±32 months) and 6-38 months (mean 15±10 months), respectively. All of the patients had received regular vitamin D therapy (0.25 g/ day) during the six months preceding the bone biopsy. Calcium carbonate was used as the primary phosphate binder (0.15 mg/kg/day); none of the patients had received aluminium hydroxide therapy.

Transiliac bone biopsies were performed using the standard technique described earlier (5). Biopsies were obtained using a disposable "J" type bone marrow biopsy needle (Manan Medical Products, Inc., Northbrook IL, USA). Patients tolerated the procedure well without any complications. In vivo tetracycline labeling could not be performed. Specimens were fixed in 8% formic acid followed by 2 hours wash under tap water for decalcification. The specimens were then processed routinely and paraffin blocks were prepared. Five micron-thick sections were cut and stained with hematoxylin and eosin. On the basis of the histology, the biopsies were classified according to the following criteria:

a. normal bone biopsies: no evidence of increased or decreased bone turnover and normal osteoid distribution and thickness;

b. high turnover bone disease: general increase in osteoblastic and osteoclastic activity with increased osteoid tissue, resorption cavites, areas of woven bone and peritrabecular fibrosis;

c. low turnover bone disease: decrease in osteoblastic and osteoclastic activity with flat osteoblasts, few osteoid seams and rare osteoclasts and no resorption cavities;

d. mixed bone disease: a combination of high and low turnover bone disease.

Blood samples for the determination of biochemical parameters were obtained during the same week in which bone biopsy was performed. Serum calcium, phosphate and total alkaline phosphatase were measured by standard automated techniques. Intact PTH (iPTH) was measured by immunoradiometric assay (Nichols Institute, normal range 12-72 pg/ml).

Images of hand X-rays were obtained using a mammographic technique. All X-rays were examined by two different radiologist blinded to histology. Acro-osteolysis of the terminal phalanx and subperiostal erosions were considered as radiological evidences of high turnover bone disease

Statistical analysis

All results were expressed as mean ± SD. Student's t test was used to compare two independent proportions. The predictive value of iPTH concentration for the histological diagnosis of the bone lesion was expressed in terms of sensitivity and specificity (6).

RESULTS

High turnover bone disease (Fig.1) was the most common type of ROD present in 8 of the 17 patients. Of the remainden, 5 patients had LTO bone disease (Fig. 2) and 4 had mixed lesions (Fig. 3) of ROD.

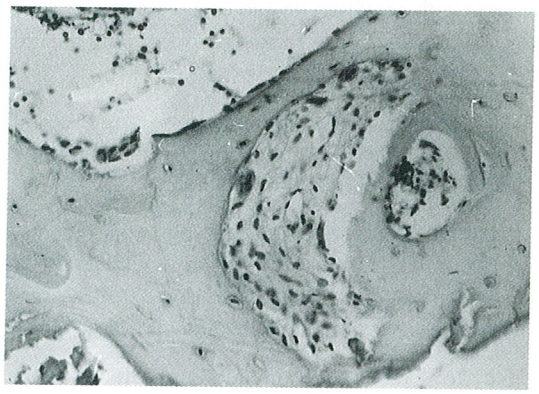

Fig. 1 : High turnover bone disease characterized by peritrabecular fibrosis and osteoclastic resorption with increased osteoblastic activity (H&E; x 100).

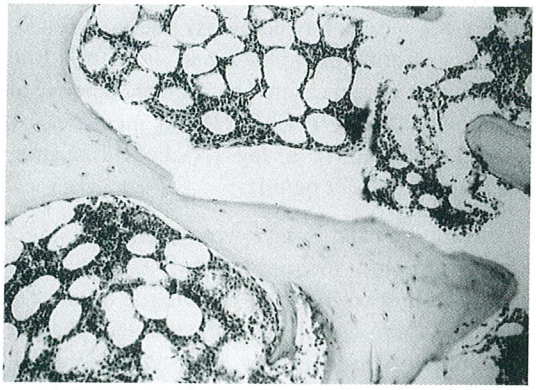

Fig. 2 : Low turnover bone disease with no fibrosis and very few osteoblasts around bony trabeculae (H&E; x 100).

Patient characteristics and laboratory features of the study group are shown in Table 1. Seven of the patients who had tubulo-interstitial nephritis were found to have HTO bone disease. None of the patients with glomerulonephritis had HTO bone disease, 2 had LTO and 2 had mixed lesion of ROD. Mean age of the patients with HTO bone disease was higher than the patients with LTO bone lesion ($p<0.05$) (Table 2).

Serum calcium levels were decreased in all groups except in the patients with LTO bone disease. Mean serum calcium levels were significantly higher in the LTO groups, compared

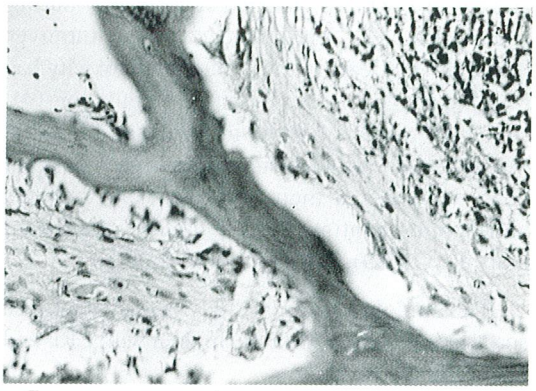

Fig. 3 : Mixed bone lesion showing the features of osteitis fibrosa and osteomalacia (H&E; x 100).

to the patients with HTO bone disease ($p<0.001$). Mean serum iPTH levels were raised in all subgroups except those with LTO bone disease. All patients in the HTO bone disease group and 3 of the 4 patients who had mixed bone lesions were found to have serum iPTH>200 pg/ml. However, none of the patients with LTO bone histology had a serum iPTH>200 pg/ml. In the diagnosis of HTO bone disease, a serum iPTH>200 pg/ml had a sensitivity of 100% and specificity of 66%. Five of the 8 patients with HTO bone disease had radiologic evidence of hyperparathyroid bone disease.

DISCUSSION

Bone disease is one of the most important complications of CRF and it represents a spectrum of skeletal disorders that ranges from HTO to LTO bone lesion. The prevalence of different types of ROD varies markedly between centres due to differences in the diagnostic criteria used to identify bone disease. The biochemical parameters are relatively poor predictors of the type and severity of bone disease. Although bone biopsy still represents the most sensitive diagnostic method, it is an invasive procedure and it must be used for research purposes or for selected patients.

The results of our study indicate that HTO bone disease remains the most frequent type of bone disease in children undergoing CAPD. Children who are at particular risk to HTO bone disease include those with a long history of renal impairment and those with predominantly tubulo-interstitial forms of renal disease. We suggest that

Table 1: Patient characteristics and laboratory parameters.

No	Age (years)	Primary disease	Diagnosis of CRF (months)	Time on CAPD (months)	Time on ROD therapy (months)	Calcium (mg/dl)	Phosphate (mg/dl)	Alkaline Phosphatase (IU/l)	iPTH (IU/l)	Radiology
					HIGH TURNOVER BONE DISEASE					
1	15	TIN	6	6	6	7.7	6.0	626	2052	N
2	11	Cystinosis	29	24	24	9.7	9.2	2835	1815	Active ROD
3	14	TIN	6	6	6	7.2	9.5	1740	1246	Active ROD
4	20	TIN	120	6	43	7.9	9.6	149	1219	N
5	16	TIN	96	6	24	7.4	7.1	145	711	N
6	11	TIN	46	31	39	9.2	8.9	525	1038	Active ROD
7	18	TIN	77	6	66	8.2	6.9	1605	227	Active ROD
8	14	TIN	56	21	43	6.6	6.6	744	674	Active ROD
					LOW TURNOVER BONE DISEASE					
1	10	Cystinosis	23	6	22	11.2	1.8	295	29	N
2	7	HUS	24	10	18	11	3.4	122	3	N
3	13	TIN	40	38	38	8.6	11.3	102	10	N
4	14	J Nephronophthisis	72	10	72	11.8	2.8	325	23	N
5	10	HUS	35	14	33	13	5.3	127	51	N
					MIKST BONE DISEASE					
1	15	RPGN	26	15	15	9.3	4.5	283	293	N
2	15	Alport Syndrome	21	17	17	7.3	7.5	131	226	N
3	13	TIN	27	27	27	9.4	6.3	168	225	N
4	10	FGS	17	6	16	8.1	7.1	76	78	N

TIN: Tubulo-interstitial Nephritis, HUS: Hemolytic Uremic Syndrome, RPGN: Rapidly Progressive Glomerulonephritis, FGS: Focal Glomerulonephritis

patients with tubulo-interstitial nephritis are less symptomatic and the duration between the onset of the disease and time of diagnosis is long. As they do not receive therapy, bone disease worsens with the progression of renal disease. In addition, hypophosphotemic and chronic acidosis might be some important factors in HTO bone disease of patients with tubulo-interstitial nephritis. On the other hand, patients who had a more rapidly progressive course of renal pathology might have a lower risk of developing HTO bone disease at the beginning of CAPD.

The LTO bone lesion has been an increasingly described histological pattern in patients undergoing CAPD (4,7-11). In our study, 5 of our seventeen patients were found to have LTO bone disease. The ages of the patients with LTO bone disease were found to be lower as compared to the children with HTO bone lesion. The duration of CAPD and ROD therapy was similar in both groups. However, the duration of CRF was found to be shorter in children with LTO bone disease than patients with HTO bone disease. Moreover, the duration between the diagnosis of CRF and the onset of ROD therapy was also found to be shorter in patients who had LTO bone lesion. These results indicate that even routinely prescribed regular vitamin D therapy early in the course of the disease may lead to LTO bone disease in small children who have CRF due to rapidly progressive forms of renal pathology.

The results of our study have demonstrated that decreases in serum iPTH levels correlated with the histological evidence of LTO bone disease. Conversely, serum iPTH levels > 200 pg/ml were 100% sensitive but only 66% specific for patients with HTO bone disease. On the other hand serum calcium levels were higher in the patients with LTO bone disease.

The primary goals of therapy for children with ROD are to return bone formation toward normal and to bring biochemical parameters within a range that corresponds to a normal rate of skeletal remodelling. However care must be taken to avoid misinterpretation of normal biochemical levels as indicators of normal bone turnover and mineralization in small children on CAPD.

In conclusion, many children on CAPD are routinely prescribed ROD replacement therapy

Table 2 : Comparison of histological and biochemical data of the patients (Results are shown as mean ± SD. Reference values and units for each parameter are indicated).

	HTO	LTO	Mixed	Total
N	8	5	4	17
Age (years)	14.8 3.1*	10.8 2.7	13.2 3.0	13.2 3.2
Diagnosis of CRF (months)	54.5 41.3	38.8 19.9	22.7 4.6	42.4 31.9
Time on CAPD (months)	13.2 10.3	15.6 12.8	16.2 8.6	14.6 10.2
Time on ROD therapy (months)	31.4 20.4	36.6 21.3	18.7 5.56	29.9 18.6
Calcium (8.1-10.5 mg/dl)	7.98 1.03	11.1 1.6 † ¥	8.5 1.0	9.0 1.8
Phosphate (2.6-5.5 mg/dl)	7.97 1.46	4.92 3.78	6.35 1.30	6.69 2.58
Alkaline Phosphatase (38-145 IU/L)	1046 937	194 106	164 87	588 766
iPTH (12-72 pg/ml)	1122 603 §	23 18	205 90	583 663

HTO: high turnover LTO: low turnover

* $p<0.05$ vs LTO bone disease

† $p<0.01$ vs HTO bone disease

¥ $p<0.05$ vs total patients

§ $p<0.01$ vs LTO bone disease

with vitamin D compounds and calcium carbonate, irrespective of their ages, primary diseases and duration of CRF and sometimes even biochemical parameters. However, there is not much experience with the use of ROD therapy in early renal failure, especially in small children who have rapidly progressive forms of renal diseases. Although HTO bone disease is still the most common type of ROD in children, it has become clear that routine therapy is not necessary in every case and may simply contribute to LTO bone disease in the young and growing skeleton of small children undergoing CAPD.

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