ORIGINAL ARTICLE

The Spectrum of Renal Osteodystrophy: A Clinical, Biochemical, Radiological and Histopathological Study

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Abstract

The chief mineral source of Jammu province is bauxite, an aluminium ore, so a possibility of water being heavily polluted with aluminium is prevalent. Hence, in an effort to relate this regional geographical aspect with aluminium bone disease (ABD) in chronic renal failure (CRF), 50 cases of CRF were prospectively evaluated. Patients were subjected to a thorough history and clinical examination. Biochemical parameters along with raiological skeletal survey and iliac crest bone biopsies were undertaken. Sixty-eight per cent of CRF patients were also consuming aluminium containing phosphate binders (ACPB) at that time. The study revealed an occurrence of ABD in 10% of CRF patients. It was found predominantly superimposed upon osteomalacia (8%) and mixed osteodystrophy (2%). Superimposed ABD on osteomalacia was found more frequently in pre-dialysis (10.8%) than after haemodialysis group (7.69%). Moreover, the incidence of ABD superimposed on osteomalacia and mixed osteodystrophy was higher in the ACPB group (14.7%) than the post-haemodialysis group (7.69%). Correlating, the pre-dialysis, post-haemodialysis and ACPB ingestion status of CRF patients on one hand and histologically proven ABD on the other, it was deduced that the majority of cases of CRF having ABD was seen in ACPB ingestion group (14.7%) followed by pre-dialysis (10.8%) and post-haemodialysis (7.69%) groups. Thus it was concluded that in the present work, ACPB ingestion was the major source of aluminium deposition in bones of patients with CRF rather than the water used in dialysis or possible pollution of drinking water with aluminium in our province.

Key Words

Chronic renal failure; Renal osteodystrophy; Aluminium intoxication; Aluminium bone disease (ABD)

Introduction

The spectrum of renal osteodystrophy (ROD) includes a number of morphological alterations in skeleton such as osteoporosis, osteosclerosis, mixed uraemic osteodystrophy, aplastic bone disease, marrow fibrosis, osteoclastoma, periosteal neosteosis, amyloidosis and the more recently "aluminium bone disease" (ABD) having distinct clinical, radiological and histopathological diagnostic features.

The increased body aluminium (Al^{3+}) is a common problem in end stage renal failure (ESRF) which has been extensively documented in individuals (1) on long-term haemodialysis (where the source of Al^{3+} has been the water used for dialysate preparation) and those taking aluminium containing phosphate binders (ACPB), used therapeutically for decreasing phosphorus absorption (2, 3). The possibility of accidental Al^{3+} contamination by other than oral route has been difficult to exclude.

Al^{3+} has a cumulative effect, thus even short-term exposure to Al^{3+} in phosphate binder adds to the total

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load and may contribute to the risk of Al^{3+} related bone disease. Al^{3+} has a direct effect, inhibiting bone formation and resorption and an indirect effect through its action on parathyroid hormone synthesis and by its modulation of calcium activity (4). Only the stainable aluminium at the mineralization front reflects the histopathological changes observed in bone. So the bone biopsies remain the only approach for definitive diagnosis of aluminium related bone disease. The specific location of Al^{3+} in bone is more important than overall organ concentration (5). The chief mineral source of Jammu province is bauxite, an aluminium ore, so a possibility of water being heavily polluted with aluminium is prevalent (6). Hence, in an effort to relate this regional geographical aspect with aluminium bone disease in CRF patients in Jammu, in this study 50 cases of CRF were prospectively evaluated over a period of one year.

Materials and Methods

Fifty patients of CRF diagnosed by relevant clinical and investigative criteria were enrolled in this study. The diagnosis of renal osteodystrophy (aluminium bone disease) in these subjects was based on clinical symptoms and signs, radiological and histopathological evidence. Cases of bones diseases due to non-renal causes were excluded. A detailed history and physical examination was recorded on a specially prepared proforma and the investigations carried out included:-

(i) Haemogram, urinalysis and ECG.

(ii) **Biochemistry :** urea, creatinine, sodium, potassium, phosphorus, calcium, blood sugar (F), alkaline phosphatase, uric acid, lipid profile and serum proteins.

(iii) **Radiography :** (a) Skull - lateral view; (b) Wrists & Hands - AP view; (c) Dorsolumbar spine - AP view; (d) Pelvis - AP view; (e) Chest - PA view; and (f) Rapid sequence infusion pyelogram (where required).

(iv) **Ultrasonography:** For kidney and parathyroid gland size.

(v) Percutaneous renal needle biopsy (where required).

(vi) Percutaneous iliac crest needle biopsy for bone histopathological study by using a modified Von-kossa method, H&E and Aluminon stains.

Results

The study revealed a total of 17 cases of histopathologically positive renal osteodystrophy (ROD), out of which only 7 had initial bone symptoms and signs. The most frequent being diffuse bone pain (82.35%), bone tenderness and muscular weakness (47.05% each).

Interestingly, of the three bone disease patterns viz., osteomalacia 10 (58.82%), osteosclerosis 4 (23.52%) and mixed osteodystrophy 3 (17.64%) was found out of the 17 ROD cases. ABD was found superimposed on osteomalacia 4 (23.52%) and mixed osteodystrophy 1 (5.88%) only. In other words, a total occurrence of ABD in 10% of CRF patients and in 29.4% of histopathologically positive ROD cases, being predominantly superimposed on osteomalacia (8%) and mixed osterodystrophy (2%). All cases of ABD had radiological evidence of renal osteodystrophy. Soft tissue calcification (7.69%), peri-articular calcification (7.69%) and fractured vertebrae (7.69%) were seen in addition to the other raidological features of ROD. On histopathological examination, ABD was seen as spots of aluminium with no apparent osteoid seams (Fig. 1) or as dark black aluminium lines at osteoid mineralized bone interfaces (Fig. 2).

The pre-dialysis, post-haemodialysis and ACPB ingestion status of the patients also had a variable prevalence in the histopathological type of ROD (Table 1), with ABD as a whole being more prevalent in ACPB ingestion group (14.70%) but predominantly more common (10.81%) in predialysis patients having osteomalacia than those in post-haemodialysis group (7.69%).

In ABD, the elevated serum alkaline phosphatase was seen in 9.09% of patients of osteomalacia and 9.09% of mixed osteodystrophy; hypocalcemia in 9.67% and 3.22% and hyperuricemia in 10.25% and 2.56% of said cases. The creatinine clearance was calculated for CRF patients and all patients having histopathologically positive ROD had creatinine clearance <40 ml./minute.

Etiological diagnoses of CRF showed that in chronic glomerulonephritis, the ABD was seen in 14.2% cases of osteomalacia and 7.14% of mixed osteodystrophy, whereas in diabetic nephropathy ABD was seen in 15.38% cases of osteomalacia. ABD was seen in 40% of the diabetics in comparison to 60% in the non-diabetic patients having CRF. In patients having encephalopathy, ABD was seen in 40% of cases.

Group	CRF (n=50)		Histopathological types of ROD									
			Osteomalacia		Osteosclerosis		Mixed Osteodystrophy		Aluminium Bone Disease			
									Osteomalacia		Mixed Osteodystrophy	
	Pts	%	Pts	%	Pts	%	Pts	%	Pts	%	Pts	%
Pre-dialysis	37	74	7	18.19	3	8.10	2	5.40	4	10.81	--	--
Hemodialysis	13	26	3	23.07	1	7.69	1	7.69	1	7.69	--	--
ACPB Ingestion	34	68	7	20.58	3	8.82	3	8.82	3	8.82	2	5.88

Table 1 : Relation of the therapeutic status of CRF patients with histopathological types of ROD (Renal Osteodystrophy).

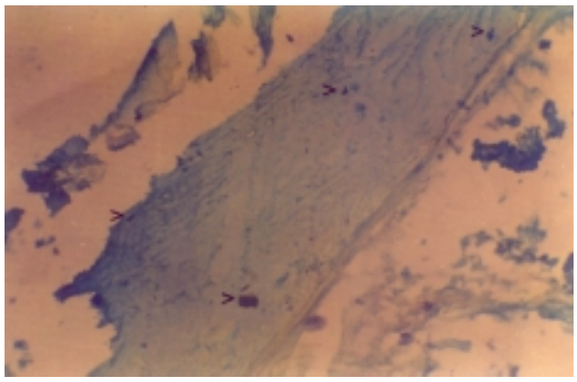

Fig. 1 :- Microphotograph showing undecalcified section of iliac crest bone biopsy showing aluminium deposits as specs or spots (>) inside the mineralized bone-diagnostic of Aluminium Bone Disease. (Aluminon stain x 100).

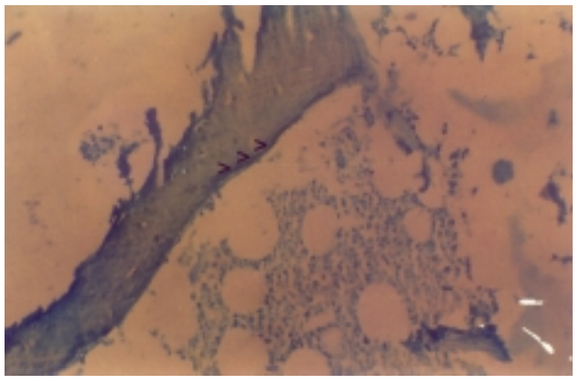

Fig. 2 :- Microphotograph showing undecalcified section of iliac crest bone biopsy showing aluminium lines (dark-reddish brown) (>>>) at osteiod (light blue), mineralized bone (light green) interface characteristic of Aluminium Bone Disease.

Discussion

Renal osteodystrophy is a metabolic complication of chronic renal failure. The long standing alterations in the mineral metabolism generated by renal failure have a profound effect on skeleton and induces a severe systemic disease (7). It is the 3rd commonest cause of metabolic disease in developed countries (8), but much information from developing countries is not available (9).

The low prevalence of ROD in tropics differ strikingly from reports in temperate areas and it varies according to the centre, region, countries and duration of renal pathology, regional sunlight exposure, dietary habits and perhaps the ethnic anecdoctal variation in bone constitution (10).

In Jammu province, bauxite deposits are found in Reasi at Chakhar, Panhansa, Salal, Jangalgali and Sukhwal gali. Al^{3+} is extracted from the bauxite (7). These geographical peculiarities of the province could have a relation with ABD considered in the present study. Jammu district is the most populous district of the province (7) and greater number of patients (89.2%) of ROD belonged to this district.

In western countries, as reported by Malluche (11), aluminium bone disease is found in 50% of unselected cases of CRF, in 90% cases of osteomalacia and 50% in mixed osteodystrophy (MOD) depending upon exposure to Al^{3+}.

In comparison, the present study showed 10% of unselected cases of CRF having ABD and 8% having ABD superimposed upon osteomalacia and 2% on mixed osteodystrophy. The overall prevalence of ABD in present study is lower than all reports except one by Joffee *et al* (12). (Table 2), in which a prevalence of 8% has been reported. Coburn reported a low frequency of osteomalacia in areas where the water content is not polluted with aluminium (13). Pierdes *et al*. (14) stated that the commonest feature of ROD in USA is osteitis fibrosa while in part of

UK osteomalacia predominates. In India, Rao *et al* (15), reported that out of 50 ESRD patients, 32 had renal osteodystrophy of which 4 had ABD whereas in present study, out of 50 CRF cases, 17 had ROD out of which 5 had ABD which is a relatively higher prevalence in comparison.

The present study showed osteomalacia (20%) as the predominant type of bone disease followed by osteosclerosis (8%) and MOD (6%) and ABD was seen predominantly superimposed upon osteomalacia (8%) and MOD (2%) and in glaring contrast, the pure hyperparathyroidism disease (osteitis fibrosa) and aplastic bone disease have not been seen in the ROD patients.

Malluche *et al* (11), Ward *et al* (16), Cournot *et al*. (17), reported that Al^{3+} deposition in bone characteristically induces low turn over type of bone disease (osteomalacia) though it has been reported in other histological types. In the present study, 68% of CRF patients were consuming aluminium containing phosphate binders (ACPB) for a period ranging from 6 months to 12 years (mean 2.92 ± 2.44 years) out of which 41.17% developed ROD out of which 8.82% had ABD superimposed on osteomalacia and 5.88% on MOD. So the total percentage of patients consuming ACPB who developed ABD was 14.70%.

The reverse osmosis was used in cases reported by Rao *et al* (15). In the present study neither reverse osmosis nor deioniser was used in haemodialysis and 13 out of 50 patients were on haemodialysis for period ranging from 6 months to 2 years (mean 0.92 ± 0.64 year), out of which 38.4% developed ROD and 7.69% developed ABD superimposed on osteomalacia which is a relatively lower percentage in comparison to ACPB group in which ABD was seen in 14.70%. So ABD has apparently a strong association with patients consuming ACPB in this study, an observation similar to that reported by Rao *et al* (15).

Further, in an effort to relate the regional geographical aspects with ABD in the present study, it is a well known fact that the chief mineral source of Jammu province is bauxite, an aluminium ore. So there could be a possibility of water being heavily polluted with Al^{3+} in Jammu province. Al^{3+} induces a low turnover type of bone disease (osteomalacia). The province has the majority of ROD patients having osteomalacia with the predominance of ABD in this group.

In the present study, the pre-dialysis patients were 74% of total CRF patients, out of which ROD was present in 32.43% and ABD in 10.8%. Correlating, the pre-dialysis, haemodialysis and ACPB ingestion status of CRF patients on one hand and the histological types of bone disease on the other hand, it can be logically deduced that the majority of CRF patients having ABD were seen in ACPB ingestion group (14.70%) followed by pre-dialysis (10.8%) and haemodialysis group (7.69%). Thus it can be deduced that ACPB ingestion was the main source of Al^{3+} deposition in bones in patients of CRF in the present study rather than the water used in dialysis or the possible pollution of drinking water of the province with aluminium.

Ward *et al* (16) & Parkinson *et al* (18) reported bone pain, myopathy and multiple fractures in 30% of dialysis patients from certain areas in England where water content of aluminium was more than 75 to 100 microgram per litre. In the present study, bone pain was seen in 31.25%, proximal myopathy in 20% and fractures were not seen in any dialysis patients from Jammu province.

Chazan *et al* (19), Sprague *et al* (20) & Martyr (21) reported a relationship between body aluminium accumulation and neurocognitive dysfunction or morbidity in patients of CRF. In the present study, 40% of the patients having ABD had encephalopathy.

Pei *et al* (22) studied ROD in 259 diabetic patients and observed that osteitis fibrosa and MOD were seen uncommonly (8 patients) and aplastic bone disease was more commonly seen (19 patients) and ABD was more commonly seen in non-diabetics. In the present study, the osteitis fibrosa, MoD and aplastic bone disease were not seen in the diabetic, however, 3 out of 13 diabetic patients having CRF had histological evidence of osteomalacia; 1 out of 13 patients had osteosclerosis and 2 out of 13 had ABD superimposed on osteomalacia. The ABD was seen more in non-diabetics (3 out of 13 patients) than in the diabetic patients. ABD was seen in 40% of the diabetic in comparison to 60% in the non-diabetic patients.

Malluche *et al* (11) reported that in mild to moderate renal failures at GFR <40 ml per minute, woven osteoid is present and impaired mineralization is seen at osteoid surface in some patients. Smith *et al* (23) state that in ESRF all patients have abnormal histology and apparently 5% have stainable Al^{3+} at the mineralization front. In the present study, all patients having histopathologically positive ROD had creatinine clearance or GFR <40 ml per minute with histological spectrum as shown in Fig. 3.

Group		Percentage of histopathological types of renal osteodystrophy								
							Aluminium Bone Disease in			
Author	Year of Study	Osteo-malacia	Osteitis fibrosa	Osteo-sclerosis	Mixed Osteo-dystrophy	Aplastic Bone Disease	CRF	Osteo-malacia	Mixed Osteo-dystrophy	Osteitis fibrosa
Ellis & Peart (24)	1973	--	80.90	30.0	20.40	--	--	--	--	--
Mankin HJ (25)	1974	--	--	20.0	--	--	--	--	--	--
Joffe P *et al* (12)	1989	--	--	--	--	--	8	--	--	--
Malluche HH *et al* (11)	1990	5.35	5.30	--	45.80	--	50	90.00	50.00	--
Loernzo Sellare V *et al* (26)	1991	14.0	30.00	--	11.00	--	--	7	50.00	--
Huraib S *et al* (27)	1993	--	66.00	--	--	--	--	--	--	60.00
Sherrard DJ *et al* (28)	1993	--	62.00	--	--	--	--	--	--	--
Mathias R *et al* (29)	1993	--	23.80	--	19.04	28.57	19.04	--	--	--
Rao M *et al* (15)	1993	20.00	--	--	44.00	--	--	3.00	9.50	--

Table 2 : Comparative study of histopathological positivity and types of renal osteodystrophy.

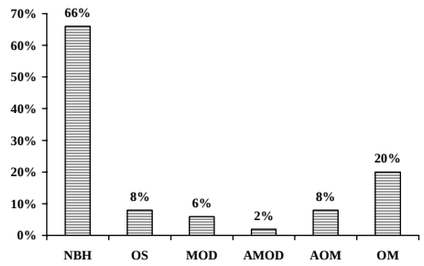

Fig. 3 : Histopathological features of ROD in CRF shown as percentage.

NBH - Normal Bone Histology
OM - Osteomalacia
AOM - Aluminium bone disease in OM
AMOD - Aluminium bone disease in MOD
MOD - Mixed osteodystrophy
OS - Osteosclerosis

Conclusion

It was concluded that as compared to western countries where ABD is found in nearly 50% of unselected cases of CRF and in 90% cases of osteomalacia and 50% in mixed osteodystrophy depending upon exposure to aluminium, the present study showed only 10% of unselected cases of CRF having ABD, 8% having ABD superimposed on osteomalacia and 2% on mixed osteodystrophy. It was further deduced that ACPB ingestion was the main source of aluminium deposition in bones of CRF patients, rather than the water used during dialysis or possible pollution of drinking water in Jammu province.

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