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Research Article

CLINICAL PROFILE OF MINERAL BONE DISORDERS (RENAL OSTEODYSTROPHY) IN CHRONIC KIDNEY DISEASE PATIENTS

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ABSTRACT

Objective: The objective of the study was to evaluate the clinical profile of mineral bone disorders (renal osteodystrophy) in chronic kidney disease (CKD) patients.

Methods: A retrospective study was performed involving 100 patients above 15 years of age with previously diagnosed chronic renal failure. A series of tests such as biochemical, radiological, and arterial calcifications were monitored. The mean age of subjects in our study was 52.54 years.

Results: Biochemical tests revealed that hypocalcemia was present in 54% of the patients, and hyperphosphatemia was seen in 84% of the participants, while only 22% of the participants had high alkaline phosphate (ALP) levels. Radiological tests revealed that 39 patients had aortic calcification, 42 patients had radial artery calcification, and 27 patients had both. Subperiosteal resorption was seen on 29 participants. The majority of the vascular calcification and subperiosteal resorption was seen in patients with CKD Stage 5, and both aortic and radial artery calcifications were significantly associated with subperiosteal bone resorption.

Conclusion: The results point toward a high prevalence of derangement in the mineral, vascular and valvular calcifications. Serum total ALP can serve as a biochemical marker to identify a pattern of bone turnover where intact parathyroid hormone is not available. The results highlight that serum phosphorus and Ca × P product levels were significantly associated with both aortic and radial artery calcifications. There was no significant association of these calcifications with serum calcium and ALP levels.

Keywords: Chronic kidney disease-mineral bone disorder, Hypocalcemia, Hyperphosphatemia, Aortic calcifications, Subperiosteal resorption.

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INTRODUCTION

Chronic kidney disease (CKD) patients commonly have disturbances in mineral and bone metabolism. They are characterized by abnormalities of calcium, phosphorus, parathyroid hormone (PTH) or Vitamin D metabolism, abnormalities in bone turnover, mineralization, abnormality in vascular, or other soft-tissue calcification. These derangements often lead to complications requiring more attention in managing CKD. Calcification in the lung can lead to impaired pulmonary function, fibrosis, pulmonary hypertension, hypertrophy of the right ventricle, and subsequent right-sided congestive heart failure. Congestive heart failure can also be due to direct calcification of the myocardium, coronary arteries, and cardiac valves, which are also associated with cardiac arrhythmias, ischemic heart disease, and death. Vascular calcifications also lead to ischemic lesions, soft-tissue necrosis, and difficulties for kidney transplantation [1,2].

Normal serum phosphorus and calcium are maintained through the interaction of two hormones produced by the kidneys: PTH and 1, 25(OH)2D (calcitriol). These hormones act primarily on three primary target organs: Bone, kidney, and intestine. When kidney function becomes impaired, such as in CKD, attempts to maintain normal serum concentrations of calcium and phosphorus fall short due to deranged metabolism and regulation of Vitamin D, PTH, and phosphatonins. As the disease progresses, the inability to maintain normal mineral homeostasis results in altered serum levels, disturbances in bone remodeling with the development of fractures, and extra-skeletal calcification in soft tissues and arteries. Conventionally, these groups of disorders have been termed renal osteodystrophy. After a consensus held under the leadership of Kidney Disease Improving Global Outcomes in October 2005, the expert panel concluded that the manifestations of mineral and bone abnormalities were so diverse and included extra-skeletal manifestations that a new systemic disorder should be defined, called CKD-mineral bone disorder (MBD). Thus, while renal osteodystrophy simply refers to the alteration of bone morphology in patients with CKD, CKD-MBD is defined as a systemic disorder of mineral and bone metabolism due to CKD, manifested by either one or more of the following: Abnormalities of calcium, phosphorus, PTH, or Vitamin D metabolism; abnormalities in bone turnover, mineralization, volume, linear growth, or strength; and vascular or other soft-tissue calcification [3]. Here, we have used the terms synonymously for simplicity.

Early stages of CKD are characterized by disordered mineral metabolism and bone disease. Progressive loss of kidney function leads to further derangements, which are targeted by various therapeutic approaches. Thus, prevention of the disturbances in mineral and bone metabolism and their management early in the course of CKD is extremely important in improving the quality of life and longevity of CKD patients. Keeping

these factors in mind, we aimed to study the clinical, laboratory, and radiological profiles of MBD (renal osteodystrophy) in CKD patients and also see the incidence of vascular calcification (aortic and radial) in CKD patients.

METHODS

A hospital-based cross-sectional study was conducted on 100 patients at Kasturba Hospital, KMC, Manipal between December 2008 and June 2010. All patients above the age of 15 who were diagnosed with CRF previously were included in the study. Patients previously diagnosed to have any other bone disease and acute renal failure were excluded from the study. Ethical clearance was obtained from KMC Manipal Institutional Review Committee. Both verbal and written consent were taken from the participants before the study. A convenient sampling technique was performed and the participation was voluntary. Demographic details and clinical history were carefully noted. All the patients underwent a detailed clinical examination before the data collection. Both biochemical and radiological investigations were done. The biochemical analysis included the determination of serum urea, creatinine, calcium, phosphorus, albumin, and alkaline phosphate (ALP). Radiological parameters included vascular calcifications (radial artery and aortic calcification) and subperiosteal resorption. Aortic calcification was seen on the chest radiogram. Radial artery calcification was seen by B-mode USG using high-frequency linear transducer. The Doppler machine used was "GE LOGIQ 700" with a probe of 5–10 MHz using gray scale evaluation. Subperiosteal resorption was assessed by bilateral hand X-ray. All the investigations were conducted under expert guidance. Patients were then categorized according to the stages of CKD.

Data were entered into Microsoft Excel and transferred to SPSS. Descriptive data were expressed as frequency, which equaled the percentage as well (n=100). Numerical values were expressed as mean ± S.D. along with their respective units. Pearson Chi-square analysis was used to see the association between categorical variables.

RESULTS

Out of 100 participants, 65 were males. The patients' mean age was 52.54 years. The majority of the patients (n=31) belonged to the age group 46–55 years. Three participants were excluded as they were lost for follow-up. The participants were categorized according to the CKD stage, where most of them belonged to CKD Stage 5 and none to Stage 1. The details of the distribution of age group and CKD stage are presented in Table 1.

Diabetic nephropathy was the most frequent cause of CKD (n=42), followed by chronic glomerulonephritis (n=23), and hypertensive nephrosclerosis (n=17).

Biochemical investigations

The mean calcium, phosphorus, Ca × P and ALP levels were 7.18±1.15 mg/dl, 6.12±1.91 mg/dl, 47.46±14.43 mg^2/dl^2, and 126±66.89 U/L, respectively. Hypocalcemia was present in 54% of the patients, and hyperphosphatemia was seen in 84% of the participants. Only 22% of the participants had high ALP levels. The distribution of the biochemical parameters is shown in Table 2.

Radiological investigations

Of the total 100 patients, 39 had aortic calcification, 42 patients had radial artery calcification, and 27 patients had both. Subperiosteal resorption was seen on 29 participants. The majority of the vascular calcification and subperiosteal resorption was seen in patients with CKD Stage 5 (Table 3). Both aortic and radial artery calcifications were significantly associated with subperiosteal bone resorption (Table 4).

Association between biochemical and radiological parameters

Serum phosphorus and Ca × P product levels were significantly associated with both aortic and radial artery calcifications. There was no significant association of these calcifications with serum calcium and ALP levels (Table 5).

Table 1: Age-wise and CKD stage-wise distribution of the study participants

CKD stage	Age-group (years)						Total
	16–25	26–35	36–45	46–55	56–65	76–85	
Stage 2	1	0	0	1	1	0	4
Stage 3	1	0	3	3	10	0	16
Stage 4	0	2	5	4	3	0	16
Stage 5	4	4	8	23	12	7	61
Total	6	6	16	31	26	7	100

CKD: Chronic kidney disease

Table 2: Biochemical parameters

Biochemical parameters	Mean±S.D.	Minimum	Maximum
Calcium (mg/dl)	7.18±1.15	5	11.3
Phosphate (mg/dl)	6.12±1.91	2.5	13.2
Ca × p (mg^2/dl^2)	47.46±14.43	17.09	92.66
ALP (U/L)	126±66.89	45	427

ALP: Alkaline phosphate

Table 3: Radiological parameters

Variables	CKD stage				Total	p-value
	Stage 2	Stage 3	Stage 4	Stage 5		
Aortic calcification	1	8	6	24	39	0.935
Radial artery calcification	2	9	7	24	42	0.913
Sub periosteal Resorption	3	7	2	17	29	0.078

CKD: Chronic kidney disease

Table 4: Association of aortic and radial artery calcification with sub-periosteal resorption

n=100	Sub periosteal resorption		Total	p-value
	Present	Absent		
Aortic calcification				
Yes	21	21	42	<0.001*
No	8	50	58	
Radial artery calcification				
Yes	24	15	39	<0.001*
No	5	56	61	

p-values obtained from Chi-square analysis. *Statistically significant

DISCUSSION

We aimed to assess the profile of renal osteodystrophy (MBD) and vascular calcification in CKD patients presenting to the nephrology and medicine department. The clinical, etiological, and laboratory profiles were also assessed. A total of 100 patients with CKD ranging from Stage 2 to Stage 4 were analyzed.

In this present study, the majority of the patients were males (65%), with a mean age of 52.54 years. Most of the patients were between 46 and 55 years. This is by following the findings from the study by Mani where 75.5% of the participants were male [4]. The mean age is quite less when compared to the developed countries where the average age is well above 60 years [5,6]. However, it is consistent with the findings from other studies done in India [7,8]. The most common

Table 5: Association of aortic and radial artery calcification with biochemical parameters

Calcification	Ca			p-value	P		p-value	Ca × p			p-value	ALP		p-value
	L	N	H		N	H		L	N	H		N	H	
Aortic														
Present	22	16	1	0.395	3	36	<0.001	6	22	11	<0.001	30	9	0.381
Absent	32	29	0		13	48		41	20	0		42	19	
Radial artery														
Present	26	15	1	0.165	0	42	<0.001	7	24	11	0.002	30	12	0.914
Absent	28	30	0		16	42		40	18	0		42	16	

p-values were obtained from Pearson Chi-square analysis. p<0.05 considered to be statistically significant, and is indicated in bold letters. L: low, N: Normal, H: High, ALP: Alkaline phosphate

cause of CKD in our study was diabetic nephropathy, followed by chronic glomerulonephritis and hypertensive nephrosclerosis. National Registry data from Japan and the USA also suggest that diabetic nephropathy is the most common cause of ESRD, accounting for 37% and 45% of the cases [9].

Laboratory profiles

Hypocalcemia and hyperphosphatemia are the common features of CKD as the kidney plays a major role in their homeostasis. In this study too, hypocalcemia and hyperphosphatemia were present in 54% and 84% of the participants, with mean levels being 7.18±1.15 and 6.12±1.91 mg/dl, respectively. About 84% were on phosphate binders. We also noticed that the prevalence of hypocalcemia progressed with the CKD stage, where more than half of the hypocalcemic patients (35% of the total study population) belonged to CKD Stage 5. Similar abnormalities of Ca and P homeostasis have been highlighted in other studies [10,11].

Serum ALP, being a marker of several bone diseases, might be an important indicator of altered bone turnover in CKD patients. We found that 28 out of the 100 CKD patients had increased ALP, while the rest were within the reference range. A study based on National Health and Nutrition Examination Survey III database showed similar Alp levels in patients with CKD and non-CKD patients [12]. However, increased ALP levels in CKD Stages 3–4 patients were independently associated with ESRD progression and all-cause mortality [13].

Vascular calcification

Vascular calcifications, especially large vessels, lead to increased cardiovascular risk and complications. In the present study, aortic and radial artery calcifications were assessed in 100 CKD patients. Of them, 39 participants had aortic calcifications and 42 had radial artery calcifications. Both aortic and radial artery calcifications were noted in 27% of the study population. A study by Ibels *et al*. reported noticed radial artery calcifications in 38% of the study population [14]. Studies that assessed calcifications in other vessels such as femoral and iliac arteries also showed a higher prevalence of vascular calcifications ranging from 31% to 48% in the CKD patients [15,16]. Furthermore, most patients with vascular calcifications (24 in both cases) were at CKD Stage 5, but the differences were not significant statistically when compared with other CKD stages. When compared with biochemical parameters, serum P and Ca × P levels, but not Ca and ALP, were significantly altered in the patients with vascular calcifications. From these findings, we can infer that hyperphosphatemia is significantly associated with vascular calcifications. These results are in accordance with other similar studies that showed an almost two-fold increase in serum phosphate levels in CKD patients as well as the development of vascular calcifications [17,18].

Sub periosteal resorption

Derangement in Ca and P homeostasis in CKD might lead to altered bone remodeling. To assess this, we evaluated the prevalence of subperiosteal bone resorption using bilateral hand radiographs. Subperiosteal bone resorption was present in 29% of the total study population. In a similar study done by Parafitt *et al*., subperiosteal resorption was found in 51% of the participants, a figure much higher than in the present study [18]. There was a statistically significant association between subperiosteal erosion and vascular calcifications (both aortic and radial). This shows that CKD patients have generalized MBD leading to both bone and vascular changes. Such seemingly paradoxical bone demineralization and vascular mineralization aspects of CKD have been discussed in various reviews [19,20].

CONCLUSION

In the present study, the major cause of CKD was diabetic nephropathy. Out of the total 100, 36% of the CKD patients had renal osteodystrophy (MBD) with 39% and 42%, having aortic and radial artery calcifications, respectively. Both vascular calcifications were seen in 27% of the study population. Hyperphosphatemia and Ca × P were significantly associated with vascular calcifications. Subperiosteal resorption was seen in 29% of the participants.

Limitations

The major limitation of our study was the small sample size. We used Doppler for studying radial artery calcification instead of CT, which might have affected the overall prevalence. Other important biochemical parameters like PTH were not studied due to financial constraints.

CONFLICT OF INTEREST

None.

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Self.

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