

BONE MARKERS IN CHRONIC KIDNEY DISEASES

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ABSTRACT

Background: Chronic kidney damage is usually irreversible leading to renal osteodystrophy. Present study was taken up to evaluate the bone markers in patients suffering from Chronic Kidney Disease. **Materials and methods:** Study was conducted on 50 patients with chronic kidney disease in them serum calcium, phosphorous, total ALP and Tartrate Resistant Acid Phosphatase were assayed. **Results:** Calcium, phosphorous and TRACP is significantly elevated in CKD patients. Total ALP is decreased in the cases. **Conclusion:** Routine estimation of simple biochemical markers of bone metabolism like calcium and phosphorous will be helpful for clinician, to rule out whether the patients condition is turning towards high turnover or low turnover disease like adynamic bone disorders, and retrospectively check the treatment given and help preventing the deterioration of the patients condition.

KEY WORDS

osteodystrophy, Chronic kidney damage, Bone Markers

INTRODUCTION

Chronic kidney disease is a global threat to health in general and for developing countries in particular, because therapy is expensive and lifelong. Chronic kidney disease is 12th leading cause of death and 17th leading cause of disability (1). Over 1 million people worldwide are alive on dialysis or with an artificial functioning graft. Incidence of CKD has doubled in last 15 years. Moreover most epidemiological data on CKD are derived from renal registries. However, most registries record data of patients who are at a late stage of kidney disease. Much less is known about the prevalence of the earlier stages of CKD. Indeed it has been acknowledged that most of the individuals at early stage of CKD have gone undiagnosed and under treated.

Chronic renal failure has been renamed as chronic kidney disease as the word 'renal' is not easily understood by the lay public, whereas the name kidney is generally well understood. The concept of

'failure' is no longer apt for a disease which has seen much medical success.

Chronic kidney disease (CKD) is accompanied by disturbances in calcium, phosphate, vitamin D, and parathyroid hormone (PTH) homeostasis that play an important role in the pathophysiology of renal bone disease. Bone is likely to be more severely affected by CKD than might be expected from normal ageing, either due to the extremes of turnover or re-modelling that occur in CKD in adults and children, or from abnormalities of modelling that occur in growing children. The increased cardiovascular morbidity and mortality observed among patients with CKD has recently been recognized to be associated with these disturbances in mineral metabolism (2).

Chronic Kidney Disease - Mineral and Bone Disorder (CKD-MBD), is a term that encompasses a constellation of abnormalities seen in progressive kidney disease that include altered levels of Ca, P, PTH, and Vitamin D, disturbances in bone modelling

and remodelling, with the associated development of fractures or impaired linear bone growth (in children), and extra skeletal calcification in soft tissues and arteries(3). Mineral abnormalities and renal osteodystrophy in CKD and, more recently, linkage of these with extra osseous calcification have been areas of intense interest and controversies. Although bone biopsy is necessary to diagnosis of renal osteodystrophy in CKD-mineral and bone disorder (CKD-MBD) classification system, this technique is not recommended of routine evaluation for this bone disease.

Bone metabolic markers, such as bone specific alkaline phosphatase and tartrate-resistant acid phosphatase isoform 5b, may be useful clinical indicator of bone turnover in CKD-MBD (20). The initial evaluation of CKD-MBD should include: PTH, Calcium (either ionized or total corrected for albumin), phosphorous, alkaline phosphatases (total or bone specific), bicarbonate, and imaging for soft tissue calcification. If there are inconsistencies in the biochemical markers, unexplained bone pain or fractures, a bone biopsy is indicated. Serum biochemical parameters are of limited diagnostic value. The parameters are relatively poor predictors of the type and severity of bone disease. However, they are somewhat more reliable as a means to identify high- or low-bone turnover states. Hence the present study was taken up to evaluate the bone markers in patients suffering from Chronic Kidney Disease.

METHODS AND MATERIALS

The present study was conducted on 50 patients with chronic kidney disease. All were taken from OPD, Nephrology department of King George Hospital. Their ages were ranging from 20- 70 yrs. No specific reference of patients was made with reference to sex. Patients with diagnosed with Chronic Kidney Disease and Patients with End Stage Renal Disease were included in the study. Patients with ARF, who underwent kidney transplantation, on corticosteroids, other immunosuppressive agents, anticoagulants or lithium, with bone tumours and Patients below 20 yrs were excluded from study.

Samples of 30 healthy age and sex matched individuals served as controls. They do not have any evidence of any renal disease, or any bone disease. Serum was separated taking precautions to avoid hemolysis. All basic investigations are done with following tests, immediately within 2-3 hrs of sample collection.

1. Serum Calcium (Arsenazo method)
2. Serum Phosphorus (Molybdate /UV method)
3. Serum Alkaline Phosphatase (p-NPP method)
4. Serum Tartrate Resistant Acid Phosphatase (Autozyme kinetic method)

The above tests were done in the Department of Biochemistry using the MIND RAY semi auto analyzer.

RESULTS

The present study comprises of 50 cases of Chronic Renal Failure and 30 healthy age & sex matched controls. The Mean Age, S.D and S.E.M of Control and Case group are $36.83 \pm 8.03 \pm 1.49$ versus $47.28 \pm 12.67 \pm 1.79$.

TABLE 1: Number of controls and cases

S.No	Types of cases	Number of persons
1	Controls	30
2	Patients on Dialysis	30
3	Patients not on Dialysis	20

TABLE 2:-Gender distribution in controls and cases

	Males	Females
Controls	19	11

Cases	34	16
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Figure 1: Distribution of Controls and Cases

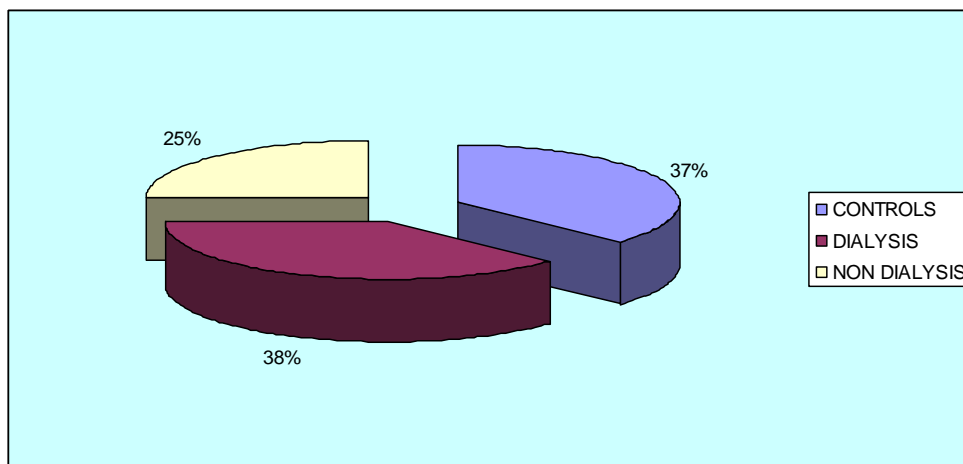


TABLE 3: Comparison between patients on Dialysis and Nondialysis group

PARAMETERS	Controls (mean ± S.D)	Cases (mean ± S.D)	p-value
SERUM CALCIUM (mg/dl)	9.55±0.8	10.36±1.4	≤0.001*
SERUM PHOSPHORUS(mg/dl)	3.24±0.8	5.10±1.01	≤0.001*
Total ALP(IU/L)	156.4±48.8	131.2±73.8	≤0.10
TRACP(IU/L)	2.20±0.5	4.6±2.3	≤0.001*

*P<0.05 is significant

TABLE 4: Comparison between patients on Dialysis and Non-dialysis group:

PARAMETERS	NON-DIALYSIS (mean ± S.D)	DIALYSIS (mean ± S.D)	p-value
SERUM CALCIUM (mg/dl)	9.78±1.67	10.77±1.04	≤0.001*
SERUM PHOSPHORUS(mg/dl)	5.67±0.79	4.6±0.95	≤0.001*
Total ALP(IU/L)	170.26±91.87	105.73±46.6	≤0.001*
TRACP(IU/L)	4.4±2.36	4.74±2.41	≤0.062

*P<0.05 is significant

Figure 2: Calcium and Phosphorus in study

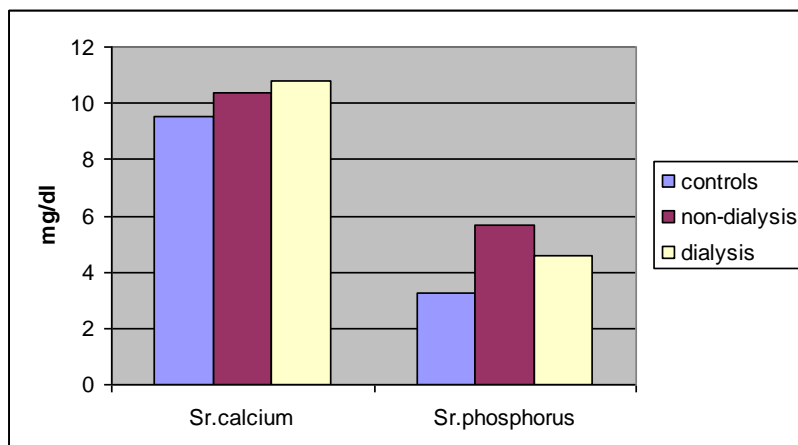
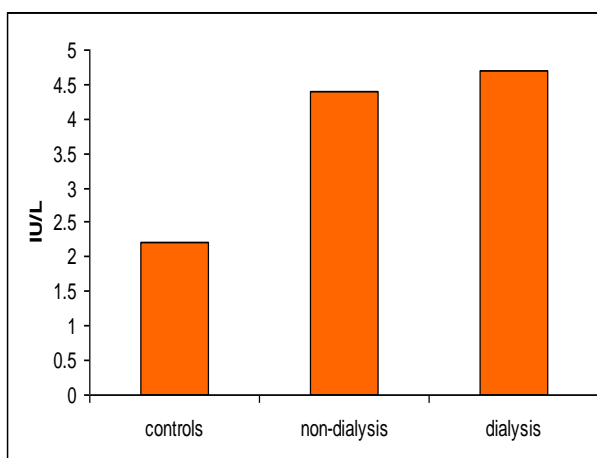
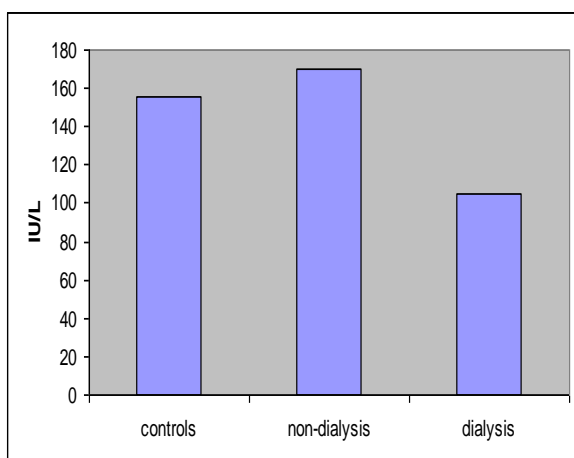


Figure 3: ALP and TRACP in study



DISCUSSION

The present study included 50 cases of Chronic Renal Disease (CRD) & 30 healthy individuals served as controls. Out of 50 cases of Chronic Renal Disease, 30 cases were on chronic dialysis and 20 cases were not on dialysis and only on conservative management. Calcium levels are significantly elevated in patients with CRD when compared to healthy controls in the present study. The elevated levels of Serum Calcium are in consistent with the following studies (4-8). Salusky, Goodman, et al, Sherrard DJ et al, Torres A, et al, Malluche H H et al, Hernandez D, Concepcion et al, Salusky, Ramirez et al, Marie Couttenye et al. The possible mechanisms of elevated calcium levels in patients with CRD could be reduced ability to incorporate serum calcium into the bone compartment(9) or Systemic exposure to calcium via the use of excessive calcium containing phosphate binders and / or active Vitamin D sterols act to decrease circulating PTH levels and depress bone

turnover(10). Or else reduced bone buffering capacity in adynamic bone, compared with other forms of renal osteo dystrophy may have additional role in pathogenesis of hypercalcemia (9, 11). Patients with lower bone turnover are less able to take up calcium could be one of the possible mechanism.

Phosphorus levels are significantly elevated in patients with CRD when compared to healthy controls our study correlates with studies (13, 14, 15, 16, 17). Brandenburg, et al, Slatopolsky EA, et al, Bryan Kestenbaum, et al, Hruska et al, Wetmore JB et al. few possible mechanism of levels of serum phosphorus in patients with CRD could be, Decreased renal phosphate excretion, Increased intake of Vitamin D or phosphate containing products , decreased PTH secretion, increased body catabolism, certain malignant, conditions, like leukemias and lymphomas or Shift of phosphate from intracellular to extra cellular fluid.

Serum Total Alkaline Phosphatase levels is lowered in Patients which is not of statistical significance. The present study is in consistent with Palmer S.C et al study (17). Total Alkaline Phosphatase levels are decreased in patients with CRD. Mechanism of lowered levels: Palmer SC et al says that it was the most consistent result of the active Vitamin D administration in patients with CRD. However recent observations showed that Plasma Bone Specific Alkaline Phosphatase (BSAP) is more sensitive than Total ALP in the evaluation of bone remodelling in CKD-MBD (18). In our study we couldnot measure bone specific alkaline phosphatase

Serum Tartrate Resistant Acid Phosphatase is also significantly elevated in patients with chronic renal disease. It is significant statistically. Serum Tartrate Resistant Acid Phosphatase is also significantly elevated in patients with chronic renal disease when compared to healthy controls. The TRACP is accurate in measuring the osteoclastic activity. TRACP activity was measured in a latest study done by Shinsuke Yamada, et al (19). They concluded that Serum TRACP may be a good marker for serum bone resorption in predialysis CKD patients, since it is not affected by renal dysfunction. Possible mechanism of increased levels of Sr. TRACP is is secreted into the circulation from osteoclasts during bone resorption (20, 21), and has been proposed as a bone resorption marker with a serum level that is independent of renal dysfunction (22-27).

Calcium values are significantly higher in patients on dialysis compared to the non dialysis group. This is in consistency with Salusky, Goodman et al. Studies. Phosphorus values are lower in dialysis group compared to patients in non dialysis group. This is in consistency with Brandenburg et al studies; probably it can be the effect of dialysis. Total ALP values are significantly decreased in Dialysis group compared to patients on Non Dialysis. This is in consistency with Palmer et al studies. TRACP values were slightly increased in patients on dialysis compared to the patients who are not on dialysis, but it was not of any statistical significance.

With further nephron loss and reduction in G.F.R, however the limits of renal reserve are exceeded and continued accumulation of urea and creatinine lead to abnormally elevated plasma concentrations. In

practice as long as the net rates of acquisition and production (i.e., liver function and muscle mass) remain reasonably constant, the inverse relationship between plasma concentrations of solutes such as creatinine and urea and GFR is sufficiently reliable and predictable to serve as clinical indices of GFR.

CONCLUSION

With prevalent administration of higher doses of Vitamin D analogs, and injudicious use of calcium supplements, low turnover form of renal osteodystrophy has become increasingly common, termed the adynamic bone disorder (ABD). ABD is not an innocent bystander in Chronic Kidney Disease (41). It is possibly the most prevalent bone lesion in advanced CKD and also patients on chronic dialysis. Though bone biopsy is the gold standard for evaluating and confirming the diagnosis of various forms of renal osteodystrophy, thus routine estimation of simple biochemical markers of bone metabolism like calcium and phosphorous will be helpful for clinician.

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