Beyond Creatinine - A Focus on Mineral Bone Disease

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Abstract: Background: Chronic kidney disease (CKD) is a term that encompasses all degrees of decreased renal function, from damaged–at risk through mild, moderate, and severe chronic kidney failure. CKD is now a public health problem affecting an estimated 10-13% of the world population. The Kidney disease: Improving global outcomes (KDIGO) define CKD as either structural or functional kidney damage or a decreased glomerular filtration rate (GFR) of less than 60 mL/min/1.73 m^2 for at least 3 months. CKD-mineral and bone disorder (CKD-MBD) is a broader, newly defined term to define the mineral, bone, hormonal, and calcific cardiovascular abnormalities occurring in CKD. Ours study aims to evaluate the prevalence CKD-MBD in CKD stages 3, 4 and 5. Material And Methods: Ours is a retrospective observational study involving Patients >18 years known cases of CKD as per KDIGO guidelines with a minimum follow up duration of 3 or more months. Result: Our study population had a mean age of 52.8 years with male preponderance (72%). All of the patients had some form of MBD present. Conclusion: Our study was able to demonstrate a very high prevalence of CKD-MBD in patients of CKD indicating a need for better understanding the factors behind MBD in Indian patients and the need to emphasize on preventing and treating MBD in patients.[Shah S Natl J Integr Res Med, 2021; 12(4): 40-44]

Key Words: CKD, Mineral Bone Disease, Calcium, Phosphorous

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Introduction: The Kidney Disease Improving Global Outcomes (KDIGO) defines CKD as either structural or functional kidney damage for at least 3 months, with implications for health[1].CKD is now a public health problem affecting an estimated 10-13% of the world population[2]. Progressive CKD is associated with adverse changes in bone-mineral metabolism. These changes begin early in the course of CKD. The term renal osteodystrophy describes the pathological changes in bone structure in CKD, however this term fails to describe adequately the adverse changes in mineral and hormonal metabolism in CKD that have grave consequences for patient survival. CKD-mineral and bone disorder (CKD-MBD) is a broader, newly defined term to define the mineral, bone, hormonal, and calcific cardiovascular abnormalities that are seen in patients with CKD. Studies suggest that these changes are associated with adverse effects on mortality resulting from vascular calcification, particularly in the coronary vasculature[3,4].

Patients of CKD stage 1 and 2 usually do not present early to health care facilities. While early detection of CKD is important to make interventions to slow the development of MBDs, early detection of MBDs in CKD can help in slowing the progression of the MBDs with worsening eGFRs. Phosphate retention and secondary hyperparathyroidism underlie the biochemical abnormalities that characterize CKD-MBD. Secondary hyperparathyroidism begins early in the course of CKD, and the prevalence increases as kidney function declines (particularly to estimated glomerular filtration rate [eGFR] <60 mL/min per 1.73 m2). Secondary hyperpara thyroidism occurs in response to a series of abnormalities that initiate and maintain increased parathyroid hormone (PTH) secretion[5].

Increased PTH concentrations first become evident when the eGFR drops below 60 mL/min per 1.73 m2. At that time, serum calcium and phosphate concentrations are normal and remain within normal ranges until the eGFR decreases to approximately 20 mL/min per 1.73 m2 or the PTH concentrations have been altered for a prolonged period of time[25]. Circulating calcitriol concentrations begin to fall much earlier, when the GFR is <60 mL/min per 1.73 m2 (occasionally even at higher eGFRs[6]), and are typically markedly reduced in subjects with end-stage renal disease (ESRD)[7]. The primary reason for the decline in calcitriol concentration is likely an increase in FGF-23 concentration, rather than the loss of functioning renal tissue[8]. Hyperphosphatemia (a relatively late pheno

menon in CKD) may also contribute to the decline in calcitriol synthesis by suppression of 1-alpha-hydroxylase enzyme.

Thus, progressive kidney dysfunction results in calcitriol deficiency and hyperphosphatemia, both of which result in hypocalcaemia. These abnormalities directly increase PTH concentrations via different mechanisms. This complex interplay has to be understood and managed well to prevent further complications down the line[4].

These biochemical alterations in turn lead to a wide variety of clinical features like bone pains, fractures, anorexia, nausea, etc[1]. The broader concept of CKD-MBD is also associated with cardiovascular calcification, poor quality of life and increased morbidity and mortality in CKD patients (the so-called bone-vascular axis).

Material & Methods: Study Design: Ours is a Retrospective Observational single center study. The data of patients who were presented at nephrolpgy and medicine department (6 months) at our institute was extracted and evaluated.

Patients who were known cases of CKD (as per KDIGO criteria who were on follow-up for >3 months) were included in the initial screening.

eGFR was calculated using the CKD-EPI (2009) equation and patients were categorized according to the KDIGO guidelines. Patients who were fulfilling the inclusion criterias, their other investigations were noted.

Eligibility Criteria: Patients aged >18 years, diagnosed with CKD according to KDIGO guidelines with eGFR <60 ml/min/1.73m^2 were included in our study. Patients with eGFR ≥ 60 ml/min/1.73 m^2, having rheumatological diseases such as rheumatoid arthritis and ankylosing spondylitis, known cases of primary endocrinological disorders like thyroid disorders, Addison's disease, parathyroid disorders, etc taking glucocorticoids, bisphosphonate, phenytoin or warfarin, History of bone fracture in preceding 6 months were excluded. Demographic details and clinical histories were noted. Serum creatinine, calcium, phosphorus and iPTH levels were noted and analyzed. All the laboratory studies were performed using standard assays at a single laboratory of our institute. The data was compiled and analyzed using Microsoft Excel and IBM SPSS 22 software.

Results : The total population studied (n) was 90 having a mean age of 52.8 ±13.2 years with the youngest patient being 25 and the oldest 84 years out of which 72.2% were male with the laboratory values being as follows.

Table 1: Laboratory Results Of The Study Patients (N=90)

	Mean ± SD	Range
Creatinine (mg/dl)	3.66 ±2.2	1.2-9.2
Corrected calcium (mg/dl)	8.3 ±0.63	6.4-9.58
Phosphorous (mg/dl)	5.13 ±1.24	3.4-8.2
iPTH (pg/ml)	319.4 ±135.7	94-650.08

The patients under stage 3, 4 and 5 were 35.6 %, 31.1% and 33.3 % respectively. A 100% of our patients had hyperparathyroidism, with none of the patients achieving the target iPTH levels as per KDIGO guidelines. Increase in iPTH levels was seen to precede the development of hyperphosphatemia and hypocalcemia.

Hyperphosphatemia in the majority of the study patients was seen to occur when the eGFR fell below ~35 ml/ min/ 1.73 m^2 and hypocalcemia in the majority was seen to occur at eGFR values less than 30ml/ min/ 1.73 m^2. None of the patients in this study showed the presence of hypercalcemia, hypophosphatemia or hypoparathyroidism.

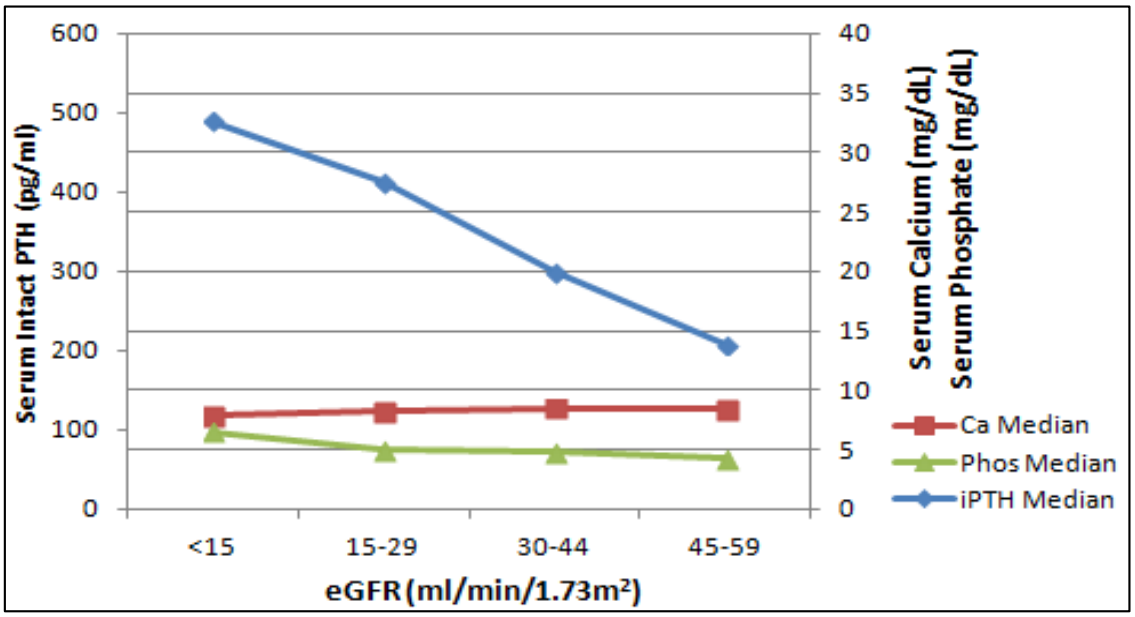
Table 2: Laboratory Parameters In Study (N=90)

Parameter	CKD 3 (N=32)	CKD 4 (N=28)	CKD5 (N=5)	CKD5D (N=25)	p value
	No (%)	No (%)	No (%)	No (%)	
Hypercalcemia (>10.2 mg/dL)	0(0)	0(0)	0(0)	0(0)	-
Hypocalcemia (<8.4 mg/dL)	11(61.4)	20(71.4)	3(60)	21(84)	<0.01
Hyperphosphatemia (>4.7 mg/dL)	16(50)	21(75)	4(80)	23(92)	<0.01
Hypophosphatemia (<2.3 mg/dL)	0(0)	0(0)	0(0)	0(0)	-

Hyperparathyroidism (>79.5 pg/mL)	32(100)	28(100)	5(100)	25(100)	<0.01
Hypoparathyroidism (<11.1 pg/mL)	0(0)	0(0)	0(0)	0(0)	-
iPTH above target range	32(100)	28(100)	5(100)	25(100)	<0.01
CKD = Chronic kidney disease;					

iPTH = Intact parathormone; Target range (<70 in CKD 3, <110 pg/mL in CKD 4 and <300 pg/mL in CKD 5D).

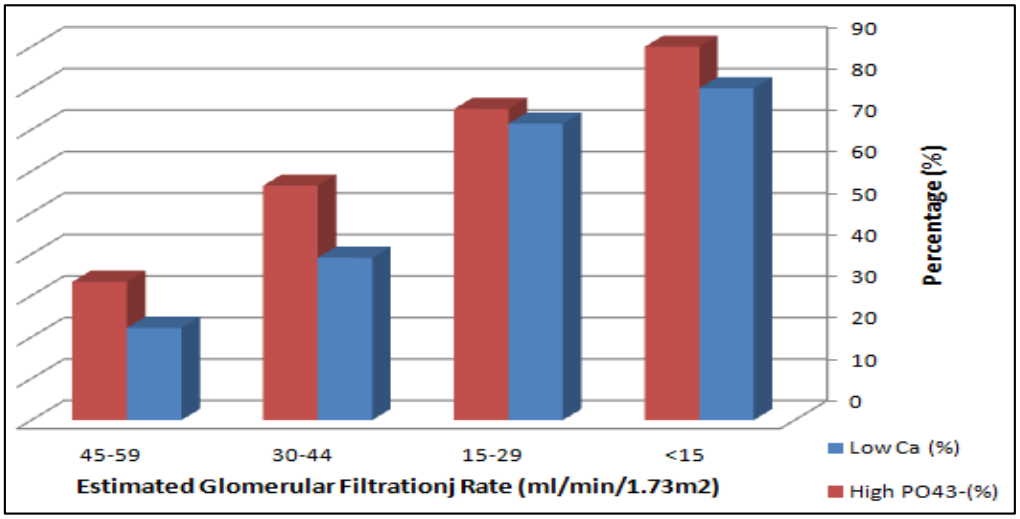
Figure 1: Median Values Of Serum Ca, P, And iPTH By eGFR Levels. Increases in iPTH Preceded Changes in Serum Ca and P.



As evidenced in Figure 1, calcium levels are significantly (Pearson coefficient r=0.464 i.e. moderately positive, p < 0.01) decreasing with a decrease in eGFR with a majority of the patients in stage 4 and 5 showing hypocalcemia.

The serum phosphate levels in the study group also increase as the stage of CKD progresses (Pearson coefficient r=0.637 i.e. moderately positive,p<0.01).

Figure 2: Prevalence Of Hypocalcemia And Hyperphosphatemia By eGFR Intervals



Discussion: Our study serves to highlight the magnitude of the problem and the need for educating the healthcare providers about MBD. There is a need to look beyond creatinine values in patients of CKD and treat other associated abnormalities like MBD as well. These are not benign and lead to increased morbidity and mortality in the form of renal osteodystrophy, atherosclerosis, accelerated worsening of eGFR, hypertension and pathological fractures. We now

know of the renal-vascular axis which leads to vascular calcification and increases the risk of adverse cardiovascular outcomes[1].

Our study also correlates well with other studies like Ghosh et al[9] with a mean age of 45.6 years with males predominating, a mean serum creatinine 4.1 mg/dl in stage 4 and 9.1 in stage 5 mg/dl; Vikrant et al[10] with a mean age of 56.8 years and males predominating, at mean serum creatinine 4.1 mg/dl; Gutierrez et al[11] with a mean age of 59.7 years and males predominating, mean serum creatinine (mg/dl) was 1.5, 1.9 and 3.2 in stage 3a, 3b and 4 plus 5, respectively.

Conclusion: As evidenced by our study patients of CKD need to be identified, characterized and regularly tested and comprehensively evaluated to pick up early MBD and treated accordingly. Treatment includes appropriate diet, supplements, medications and individualized dialysate solutions as and when needed. Our study was limited by the number of participants. There is scope for further study and research into the metabolic disorders of CKD given its wide reaching reprecussions and high prevalence.

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