Chronic Kidney Disease Mineral Bone Disorder (CKD- MBD): Further Insight at the Indian patients

The kidneys play an important role in maintaining normal serum calcium (Ca) and phosphorous (P) concentrations. Chronic Kidney Disease (CKD) is associated with significant disturbances in bone and mineral metabolism, leading to altered serum concentrations of Ca, P, vitamin D and parathyroid hormone (PTH)^{1,2,3}. These changes are initially detected when the glomerular filtration rate (GFR) falls to ≤ 60 mL/min and are nearly uniform as GFR drops to < 30 mL/min^{2,3}. This leads to a number of bone abnormalities previously called “renal osteodystrophy”, renamed as CKD-Mineral Bone Disorder (CKD-MBD) by National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF KDOQI) consensus group⁴. CKD-MBD is a systemic disorder manifested by either one or a combination of a) abnormalities of Ca, P, PTH or vitamin D metabolism, b) abnormalities in bone turnover, mineralization, volume, linear growth or strength c) vascular or soft tissue calcification. This has over time been expanded to include left ventricular hypertrophy, hypertension, immune dysfunction and inflammation^{5,6}.

CKD-MBD has been identified as major risk factor for cardiovascular morbidity and mortality in CKD patients, hence early detection and prompt management becomes imperative at achieving better survival and less risk of cardiovascular events and other complications^{6,7,8}. For CKD-MBD diagnosis and management, several global or local clinical guidelines have been published based on data from non-Asian patients especially Caucasians^{4,5}. In these guidelines, the target ranges for serum P, Ca and PTH levels are specified. Diagnosis of CKD-MBD requires bone biopsy which besides being invasive is not possible in most developing countries⁹. Hence biochemical abnormalities

are the primary indicators which guide in diagnosis and management of this condition. 2009 KDIGO guidelines and 2010 commentary agreed that the control of serum Ca, P, Vitamin D and PTH is central to the management of CKD-MBD^{5,6}. Although a specific serum Ca, P, ALP concentration at which increased risk of mortality has not been defined, there is clear epidemiologic data supporting that lower serum P, PTH is associated with better outcomes⁷.

Because of the paucity of sufficient registry data many Asian countries including India adopt global guidelines, but it is many a time difficult to apply them to local patients, as there are differences in access to diagnostic and therapeutic modalities. As these target ranges are mainly dependent on non-Asian data, they may not be optimal for Asian patients². Moreover, it is known that ethnic differences exist in skeletal resistance to PTH, which could influence the optimal target ranges⁶.

Newly detected, treatment naïve Indian CKD patients have a high prevalence of disturbances of mineral metabolism including secondary hyperparathyroidism, vitamin D deficiency, abnormal BMD, valvular and vascular calcification even before initiating dialysis^{10,11}. Spectrum of CKD-MBD has been studied in Indian CKD patients, especially in the pre-dialysis stage^{3,12,13,14}. Etta et al found a high prevalence of hypocalcemia (64.2%), hyperphosphatemia (81.1%), hyperparathyroidism (49.5%) and low Vitamin D levels (89.5%) in newly detected advanced renal failure patients; the prevalence was higher in patients with CKD stage 5 than CKD stage 4³. Low bone mass on DEXA scan and CVC and AAC calcifications were identified in a significant number of patients. Several other studies have also observed similar findings, Aggarwal described hypocalcemia in 29.9% and 49.6%;

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hyperphosphatemia in 45% and 41.8% and hyperparathyroidism in 57.8% and 39.4% in CKD stage 4 and 5 respectively¹⁰. Jabbar et al observed a prevalence of hyperparathyroidism of 60% in their patients with CKD stage 4 and 5 taking a cut-off of iPTH>300 pg/mL for both stages¹⁴. In the same study, more than 90% of patients and in another study by Ghosh et al, 83.1% of patients with CKD stage 4 and 5 had vitamin D level less than 30 ng/mL,^{11,14}.

India being a diverse country with different ethnicities and treatment availability we need to study the CKD MBD pattern across various regions of the country. More CKD patient data needs to be shared, analysed, published to establish optimal local strategies and frame respective guidelines for CKD-MBD management. Thus, establishment of locally optimal diagnostic and management strategies for CKD-MBD specific to Indian CKD patients is undoubtedly needed.

In this issue of JMS, Sheikh et al have studied the spectrum of CKD-MBD in newly diagnosed stage 3-5 CKD patients at a centre from eastern part of India¹⁵. Of the 242 patients studied, 36.8%, 46.7%, 16.5% had stage 3, 4, 5 CKD respectively. 56.8% had hyperphosphatemia ($P > 4\text{mg/dL}$), 30% had hypocalcaemia (calcium $< 8.5\text{mg/dL}$), 53.4% had vitamin D deficiency (25OH Vit D $< 20\text{ng/mL}$) and 64.9% had hyperparathyroidism (iPTH $> 65\text{pg/mL}$). They reported a significant negative correlation of GFR with phosphate, iPTH and ALP (p value < 0.001) and an insignificant positive correlation between GFR, serum calcium and 25-OH vitamin D. They concluded that CKD-MBD had a high prevalence with secondary hyperparathyroidism as the most common type and that ALP cannot serve as a surrogate marker for iPTH.

Amongst the several limitations of this study few important ones are that it is a hospital-based study in a referral centre; hence data may not reflect true community-based CKD patients. The sample size is small and one time assessment is only done, a significant flaw. iPTH cut off has been kept at $> 65\text{pg/mL}$ which may have overestimated the incidence of hyperparathyroidism. Bone histomorphometry, bone markers including fibroblast growth factor and bone-specific ALP, Bone DEXA and CT scan to accurately assess BMD and vascular calcification were not performed. Echocardiographic scoring for valvular calcification was not performed.

Yet with all its limitations this study presents the spectrum of CKD-MBD in a different region of India not previously reported. It would be prudent to have a more extensive and multicentre study to exactly know the spectrum as well as assess the effect of treatment on these abnormalities to determine any beneficial effect on long term morbidity and mortality. Also collecting more and more data from different regions of the country and then pooling and analysing the same will go a long way to frame local guidelines which may be more prudent than what is being presently followed.

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