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Review Ariticle

Mineral Bone Disorder in Chronic Kidney Disease, Mechanics and Management

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Abstract

Bone health is seriously affected in Chronic Kidney Disease (CKD). Subtle changes begin from the initial stages. Skeletal ill effects are related to imbalance homeostasis of four main players, calcium, phosphate, Parathyroid Hormone (PTH) and vitamin D. Their regulated action is important and interdependent for normal skeletal development, architectural integrity and strength. Dysregulation in these regulators result in progressive skeletal dystrophy if mechanism goes unnoticed which imparts extra skeletal deleterious effects with grave long term consequences in terms of bone pain, fractures, vascular, valvular and soft tissue calcification. Term renal osteodystrophy has been replaced by Mineral Bone Disorder (MBD) which include spectrum of diseases like adynamic bone disease, osteomalacia, osteitis fibrosa cystica, osteopenia and osteoporosis. Close surveillance with CKD stage appropriate investigations and timely action is crucial to detect and prevent skeletal and extra skeletal complications in order to minimize morbidity and mortality in CKD population with the outcome of improved quality adjusted life years. This article will help improve our understanding about the highly complex group of bone disorders in a practical and simplistic way with clinic-pathological correlation, diagnostic approach and evidence based management of MBD in a candid way.

Keywords: Adynamic bone disease; Osteitis fibrosa cystica; Osteomalacia; Osteopenia; Osteoporosis; Mineral bone disorder

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Introduction

Bone disorder usually set in at the very beginning of the CKD but clinically significant features of CKD-MBD usually starts to manifest once GFR falls below 40 due to imbalance between calcium, phosphate; PTH homeostasis [1-6].

Principally bone disorders are categorized broadly based on three parameters which include Turnover, Mineralization and Volume (TMV) [7]. High and low turnover diseases are osteitis fibrosa cystica and adynamic bone disease respectively. Mineralization defective disorders are rickets, osteomalacia. Disorders affecting bone volume include osteopenia and osteoporosis. This classification system called TMV was introduced by Kidney Disease Outcomes Quality Initiative (KDIGO) in order to improve better understanding of pathological process in the bones and to adopt corrective measures [8]. Understanding of changes occurring during bone remodeling and knowledge about the causative agents is of paramount importance to detect right disease and adopt proper intervention to achieve successful outcome.

Discussion

First abnormality is hyperphosphatemia which plays major role in bone remodeling. It is due to impaired tubular excretion of phosphate which triggers PTH as a compensatory response to off load body`s phosphate load without any noticeable effect during earlier stages of CKD. With progression of CKD, phosphate excretion diminishes further as it goes beyond the phosphaturic capacity of PTH with progressive rise in plasma phosphate resulting into hypocalcaemia and inhibition of calcitriol [9-11]. These changes result into secondary hyperparathyroidism [12-14] which contribute further to phosphate load due to mobilization of phosphate and calcium from the bone as a corrective attempt. Additionally proximal tubular phosphate reabsorption continues to rise due to its reduced excretion with progression of renal failure. Initial rise of PTH is beneficial in order to maintain phosphate balance, correction of hypocalcaemia and calcitriol but hyperphosphatemia over prolong period results into autonomous parathyroid gland with rising secretions as a consequence of skeletal resistance with advanced renal failure [11]. Hyperphosphatemia has direct stimulatory effect on PTH independent of calcium and calcitriol levels [15-18]. Another effect of hyperparathyroidism is high fibroblast growth factor 23 (FGF 23), decrease vitamin D, Calcium Sensing Receptors (CaSR), fibroblast receptors and klotho in PTH.

FGF 23 is the main factor causing low calcitriol, not reduce nephron mass [10] as a result of inhibition of enzyme 1 alpha hydroxylase which converts 25 hydroxy vitamin D to calcitriol. FGF 23 is produced from osteocytes in response to high phosphate, calcitriol and renal injury and establish its phosphaturic effect with the help of coenzyme klotho [19] to maintain phosphate homeostasis. It`s clearance is decrease in CKD. Reduced calcitriol levels stimulate PTH [20-22] by mechanism which decrease absorption from the gut and reduce mobilization from the bones resulting into hypocalcemic state triggering PTH activation resulting in release of hormone.

This phenomenon can be prevented by keeping calcitriol levels within range. An observation in a dialysis population has shown that persistent low calcitriol levels are associated with reduced vitamin D receptors within parathyroid gland which cause continuous hyper activity of the gland resulting in nodular hyperparathyroidism [23].

Calcium homeostasis is another important factor for the harmony of CKD and bone. It is maintained in a narrow range and slight disturbance result into mineral bone disorder through PTH dysregulation with grave cardio vascular consequences in terms of dysrythmias and calcifications [24,25]. Change in ionized calcium is sensed by calcium sensing receptors (CaSR) in PTH, the main regulator of calcium in the body [26]. Hypocalcemia sensed by CaSR triggers PTH to compensate this deficiency by mobilizing bone calcium by resorption [27]. CKD is usually associated with hypocalcemic state due to hyperphosphatemia, low calcitriol, and relative bone resistance to PTH. CaSR are sparse in nodular parathyroid in CKD, continuous stimulation of gland ultimately resulting into hyper phosphatemia [28-31]. High calcium phosphorous product is the basic pathology for calcifications. Worst outcome related to this abnormality is on the vasculature, especially on cardiovascular resulting into vascular and valvular calcifications [32].

Another substance which plays important role in the complex kidney bone relationship to maintain healthy equation in between is Klotho. This is a transmembrane peptide, produce from the osteocytes and acts as a cofactor for FGF23 to exert its effect [33]. Klotho continues to decrease with advancing renal failure resulting in compensatory rise of FGF23 [34,35]. Reduced klotho receptors in PTH and rising FGF 23 results into unresponsive PTH and failure of the desired outcome to suppress PTH and control phosphate balance. This situation is called skeletal resistance to PTH which contributes further to severity of secondary hyper parathyroidism. Studies have shown that high FGF 23 is associated with left ventricular hypertrophy [36] and strong association in cardiovascular morbidity and mortality outcomes in CKD [37,38]. Based on the understanding of CKD-MBD mechanism disorders of TMV becomes easier to diagnose and treat. Bone biopsy is considered gold standard for all the lesions. Bone has two important functions, maintenance of skeletal integrity and strength which is provided by cortical bone and participating in mineral homeostasis which is conferred by cancellous bone.

Osteitis fibrosa cystica is a high turnover condition due to secondary or tertiary hyperparathyroidism. Osteoclastic activity is enhanced resulting into loss of cortical bone and end-osteal fibrosis [39]. Biochemical abnormality will result into high calcium, phosphate, Alkaline Phsophatase (ALP) and PTH. Adynamic bone disease is a low turnover state which results due to suppress PTH. Osteoid activity is suppressed and there will be loss of cancellous bone with thin osteoid [40]. This condition is associated with calcifications of vessels and soft tissues. Biochemical abnormality will result into high calcium and low ALP and PTH.

Osteomalacia is a condition of defective mineralization of bone associated with low turnover state with markedly reduced osteocytes and osteoblasts [9,41]. Major factors predisposing this condition are hypovitaminosis D, hypo-phosphatemia and aluminum. Aluminum toxicity is not common now due to non aluminum calcium binders and improvement in water treatment techniques [42]. Biochemical abnormalities will be low calcium and phosphates and normal to high ALP or PTH.

Mix uremic osteodystrophy is a condition worth mentioning in advance CKD population, is a mixture of mix defect composed of abnormal mineralization associated with high and low turnover state. There is no clear biochemical abnormality for this specific condition. Cystic bone disease is a condition seen in dialysis population due to result of accumulation of beta amyloid protein over years. It is diagnosed by x ray or CT scan. Osteopenia is condition which is related to reduce bone volume. Certain risk factors predispose this condition which includes thin habitus, immobility, frailty, steroids and acidosis. There is no specific biochemical abnormality to suggest this condition. It is diagnosed by DEXA bone scan which is a measure of cortical bone volume, based on T score range. T score will differentiate between osteopenia and osteoporosis which is severely reduced bone density. These conditions are directly associated with higher fracture risk.

It is observed that with bone remodeling in CKD major event in the form of fracture usually occurs in dialysis population resulting in significant morbidity and mortality [9] because reaching this stage bone strength has compromised severely due to markedly reduced its mineral content and cortical strength due to high and low turnover mechanisms [39,40]. Different population studies has concluded that low turnover adynamic bone disease is much more prevalent disorder as compare to high turnover bone disorder [43,44].

Management Approach

Life style modification has a paramount role towards the prevention and management of bone disorders in CKD population which involves exercise, smoking cessation, reducing alcohol consumption, optimum use of calcium, vitamin D supplements and fall risk assessment and adopting preventing measures.

Hyper phosphatemia is the first culprit need to be addressed from the beginning of CKD as it is independent marker of mortality [45,46]. Aim is to keep levels within normal limits initially by patient education, dietary restrictions, later with phosphate binders, preferably non calcium based [47] and Optimization of dialysis once initiated. Refractory hyperphosphatemia to these measures is managed with holding vitamin D using calcimimetics and parathyroidectomy ultimately. These reduce intestinal phosphate absorption and PTH induced bone efflux of phosphate. Ferric citrate is another phosphate binder which has added advantage in anemia improvement [48,49].This intervention helps to control hyperparathyroidism which is the reason for osteitis fibrosa cystica. First line management of hyperparathyroidism is use of calcium, vitamin D, phosphate binders and calcimimetic. Despite optimization of these drugs if PTH levels remains beyond 800 pg/ml with skeletal dystrophic features parathyroidectomy is considered. Parathyroidectomy results in reduced fracture risks, increase bone strength, improvement in nutritional status and anemia [50,51]. A dynamic bone disease is addressed with removing Ca and vitamin D supplements from the prescription, using non calcium based phosphate binders and low calcium bath dialysate [52]. Aim is to trigger PTH secretion to help stimulate osteoblasts [42]. Teriparatide, synthetic PTH agent has come up with increase MBD in small observational studies, its use is not recommended so far [53]. Osteo penia is benefited with calcium, vitamin D preparations. Osteoporosis management is directed towards the optimization of Calcium, phosphate and PTH levels along with androgens levels and replacement as indicated [54]. Bisphosphonates orally is considered with reduced

dosages. Another option is Danusomab which has been considered safe for use in CKD and dialysis population [55].

Conclusion

To conclude this discussion it is recommended to ensure bone health by periodic monitoring of above mentioned markers of skeletal homeostasis from the earlier stages of CKD. Keep low threshold for bone biopsy. These delineate definitive diagnosis of type of osteodystrophy and guide treatment strategy. Aim to optimize calcium, phosphate and vitamin D levels. This will modulate PTH activity regulating mineralization and strength of bony skeleton and affect bone directly by regulatory bone markers, FGF 23 and klotho. Serum renal and bone markers regulate each other in a very organized manner to maintain homeostasis. Thus bone turnover is regulated based on functioning renal reserve. Avoid over suppression of PTH by excessive use of calcium based phosphate binders, vitamin D supplements and bisphosphonates as it will result into adynamic bone which has high fracture risk incidence adding further to morbidity and mortality. Adopt appropriate approach to address causes of hyperparathyroidism, medical and surgical if adenoma. Use of cinaclacet for hyper parathyroid induced osteitis fibrosa is only indicated for dialysis population [53]. Bisphosphonates are used very cautiously in advance CKD by outweighing risks against benefits. Cost affectivity and local expertise must be taken into account while considering these management options. High index of suspicion and prompt action is the key to success for dealing CKDMBD which requires understanding of pathogenesis which is quite complex but rewarding if concept employed rightly.

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