



## Association Between Bone Mineral Density and Chronic Kidney Disease: Recent Perspective

Lavanya Neerudi<sup>1\*</sup>, Keerthana Atla, Gayathri Konduri, Sireesha Vankodoth<sup>2</sup>

<sup>1</sup>Pharm D 6<sup>th</sup> year, Department of Pharm D, CMR College of Pharmacy, Kandlakoya, Hyderabad, India.

<sup>2</sup>Assistant Professor, department of Pharm D, CMR College of Pharmacy, Kandlakoya, Hyderabad, India.

\*Corresponding author's E-mail: [neerudilavanya899@gmail.com](mailto:neerudilavanya899@gmail.com)

Received: 02-01-2022; Revised: 18-02-2022; Accepted: 26-02-2022; Published on: 15-03-2022.

### ABSTRACT

Mineral metabolism and bone health are both dependent on the kidney. It is not only the major site of vitamin D activation, but it is also the target organ for different regulatory hormones such as parathormone (PTH) and fibroblast growth factor-23 (FGF-23). Chronic kidney disease (CKD) is a global health issue that affects 5–10% of the global population. Vascular dedifferentiation/calcification, osteodystrophy, loss of klotho, and high FGF23 production are all symptoms of CKD-MBD, and research into its cause is continuing. The key parameters used in standard CKD-MBD diagnosis are biochemical (calcium, phosphorus, parathyroid hormone, alkaline phosphate) radiographic (X ray, MRI scan, CT, DEXA) and bone biopsy with subsequent pathological examination. Screening for calcium, phosphorus, alkaline phosphatase (ALP), and PTH, according to KDIGO criteria, is strongly recommended. The hallmarks of CKD-MBD treatment are the correction of hyperphosphatemia, hypocalcemia, and maintaining a sufficient calcitriol concentration.

**Keywords:** Mineral metabolism; renal osteodystrophy; chronic kidney disease; Hyperparathyroidism.

### QUICK RESPONSE CODE →

#### DOI:

10.47583/ijpsrr.2022.v73i01.021



DOI link: <http://dx.doi.org/10.47583/ijpsrr.2022.v73i01.021>

### INTRODUCTION

Mineral metabolism and bone health are both dependent on the kidney. It is not only the primary site of vitamin D activation, but also the major organ for regulating some hormones, including parathormone (PTH) and fibroblast growth factor-23 (FGF-23). As a result, in chronic kidney disease (CKD), mineral metabolism becomes improper, which has an impact on bone health. The Chronic kidney disease-mineral and bone disorder (CKD-MBD) has recently been called as renal osteodystrophy (ROD)<sup>1</sup>

Renal osteodystrophy is a systemic illness caused by chronic kidney disease and metabolic bone disease (CKD-MBD) (ROD)<sup>2</sup>. The definition of CKD-MBD also include cardiovascular diseases (CVD), left ventricular hypertrophy (LVH), left ventricular dysfunction (LVD), as well as hypertension, inflammation, iron deficiency anaemia and immunological dysfunction.<sup>3</sup>

There are four identified pathological bone disorders in CKD<sup>4</sup>

1. Hyperparathyroidism (HPT) is a bone disease in which the thyroid gland produces too much parathyroid hormone. Untreated secondary osteoporosis causes a high rate of bone turnover

which is characterized by Bone abnormalities, such as cortical bone loss and irregular trabecular bone growth.

2. Adynamic bone disease is a condition in which the bones are unable to move. Bone resorption and formation are absent or poor, which could be an early sign of CKD. It is related to a low PTH level, and patients are more prone to fractures.
3. Osteomalacia is a disease affecting the bones. A poor bone turnover leads to a rise in an unmineralized osteoid matrix, resulting in a reduction in bone strength. Vitamin D insufficiency, metabolic acidosis, and hypocalcemia are frequently attributed.
4. Mixed renal osteodystrophy is a type of renal osteodystrophy that affects both the kidneys and therefore resulting in Defects in both mineralization and bone turnover.

Chronic kidney disease (CKD) affects 5–10% of the world's population, and those who have it are more likely to have bone and mineral metabolic abnormalities.<sup>5</sup> These disturbances develop a class of bone disorders known as renal osteodystrophy (ROD), which causes symptoms such as bone soreness, muscle-tendon rupture, itching and incidence of bone fractures.<sup>6</sup>

ROD patients are also more likely to develop cardiovascular calcification, which is linked to a higher risk of morbidity and mortality.<sup>7,8</sup> Regrettably, the name ROD does not include this significant extra-skeletal manifestation. As a result, the KDIGO group has proposed a new nomenclature for the systemic disorder of mineral and bone metabolism: CKD-mineral and bone dysfunction (CKD-MBD).<sup>9</sup>



Since a bone biopsy is an expensive and time-consuming procedure that involves the evaluation of tissue samples by highly qualified experts, it is rarely done. As a result, physicians rely largely on trends in parathyroid hormone levels in blood markers of phosphate, calcium, and alkaline phosphatase bone turnover to diagnose mineral bone treatment disorders.<sup>8</sup>

**Definition and classification of CKD<sup>10</sup>**

CKD is defined as abnormalities of kidney structure or function, present for more than 3 months with health consequences. (Not Graded)

**Criteria for CKD**

Either of the following present for 3months

**Table 1: CKD criteria<sup>10</sup>**

| GFR rate (decreased)                   | GFR:60ml/min/1.73m <sup>2</sup> (GFR categories G3a–G5)  |
|--|--|
| Markers of kidney damage (one or more) | Albuminuria (AER ≥30 mg/24 hours; ACR ≥30 mg/g [≥3 mg/mmol])<br>Urine sediment abnormalities<br>Electrolyte and other abnormalities due to tubular disorders<br>Abnormalities detected by histology<br>Structural abnormalities detected by imaging<br>History of kidney transplantation |

**Staging of CKD**

1. Categorizing CKD depending on the cause, GFR category, and albuminuria category.

**Table 2: CKD Categorization Based On GFR<sup>10</sup>**

| GFR category | GFR (ml/min/1.73 m <sup>2</sup> ) | Terms                            |
|--------------|-----------------------------------|----------------------------------|
| G1           | ≥90                               | Normal or high                   |
| G2           | 60-89                             | Mildly decreased*                |
| G3a          | 45-59                             | Mildly to moderately decreased   |
| G3b          | 30-44                             | Moderately to severely decreased |
| G5           | <15                               | Kidney failure                   |

2. Determine the cause of CKD based on the presence or absence of systemic illness and the location of the CKD in the kidney of Pathologic-anatomical findings that have been observed or are suspected to have occurred. (Ungraded)
3. Assign the following GFR categories (Not Graded):

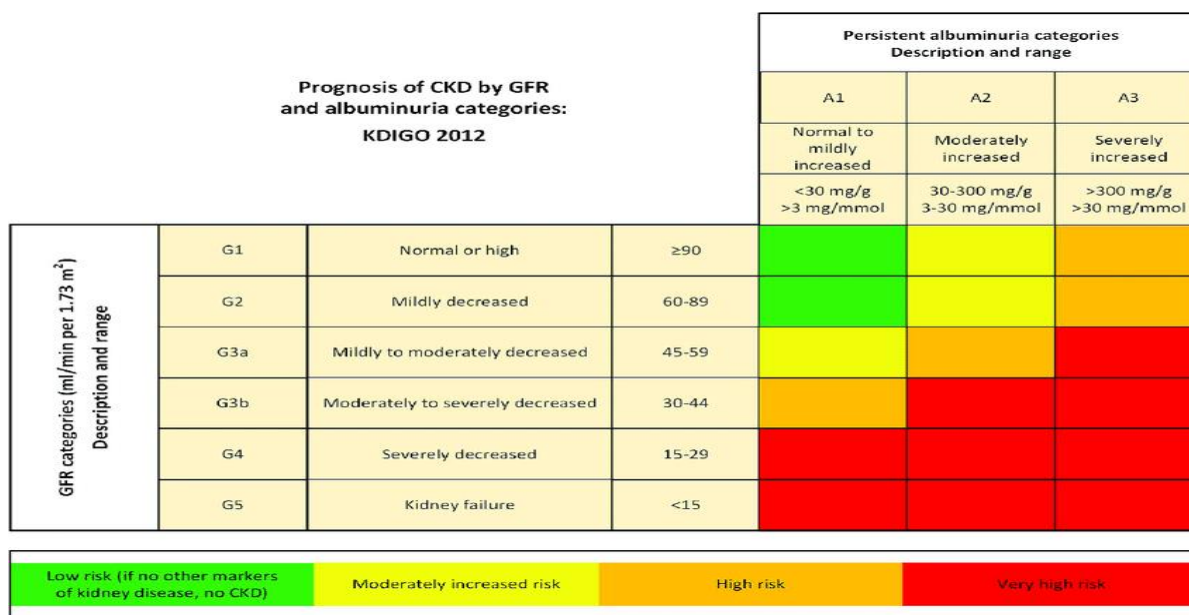
Albuminuria categories in CKD

**Table 3: CKD Categorization Based On Albuminuria<sup>10</sup>**

| Category | AER(mg\24hours) | ACR (mg\mmol) | ACR(mg\mmol) | Terms                      |
|----------|-----------------|---------------|--------------|----------------------------|
| A1       | <30             | <3            | <30          | Normal to mildly increased |
| A2       | 30-300          | 3-30          | 30-300       | Moderately increased*      |
| A3       | >300            | >30           | >300         | Severely increased**       |

\*Relative to young adult level.

\*\*Including nephrotic syndrome (albumin excretion usually ≥2200 mg/24 hours [ACR ≥2220 mg/g; ≥220 mg/mmol])



**Figure 1: Prognosis of CKD By GFR And Albuminuria Category**



## Pathogenesis

The CKD-MBD is characterized by vascular dedifferentiation/calcification, osteodystrophy, loss of klotho, and elevated FGF23 production, and research into its aetiology is ongoing.

### Role of FGF

Osteocytes synthesize FGF23, which is required for vitamin D and phosphate metabolism requires klotho (a transmembrane protein) in the kidneys and parathyroid glands to interact with the FGF receptor (FGFR).<sup>11</sup>

In the proximal renal tubule, FGF23 boosts the phosphate excretion by lowering the expression of sodium-dependent phosphate transporters in the luminal tubule, as well as possibly lowering the expression of sodium-dependent phosphate transporters in the tubule by reducing the activity of the NaPi cotransporter in the gut, phosphate absorption can be reduced.<sup>12</sup> Furthermore, it decreases 1,25-dihydroxy vitamin D [1,25(OH)2D3] production by reducing 1-hydroxylase activity while increasing 24-hydroxylase activity.<sup>13</sup> In the early stages of CKD, high levels of FGF23 inhibit 1,25(OH)2 vitamin D, causing secondary hyperparathyroidism.<sup>14</sup> Intestinal calcium absorption is reduced when serum 1,25(OH)2D3 levels are reduced. Low calcium, calcitriol, and hyperphosphatemia all aggravate excessive PTH secretion. Excess PTH causes osteitis fibrosa (weak and deformed bones) and calcium mobilization from the bones. It might also lead to deterioration of the situation.<sup>15</sup>

### Role of klotho

The Klotho gene was discovered to be a phenotype of premature multi-organ failure in mice in 1997, including shortened lifespan, stunted growth, increased thymic involution, pulmonary emphysema, cognition impairment, skin atrophy, osteopenia, ectopic soft tissue calcification, hyperphosphatemia, and high plasma fibroblast growth factor (FGF). The majority of the characteristics shown in Klotho hypomorph or knock-out animals may be restored by expressing Klotho, demonstrating that Klotho is an anti-aging gene.<sup>16</sup>

Membrane-anchored and soluble Klotho proteins appear to have different functions. Membrane Klotho is a co-receptor for FGF23, a bone-derived phosphate that promotes renal phosphate excretion and generates a negative phosphate balance. Klotho soluble is a pleiotropic protein that operates as an endocrine factor in the kidneys and elsewhere. Nuclear Klotho and cytoplasm Klotho have recently been identified to be bioactive molecules that protect cells from aging and apoptosis, according to several studies.<sup>16,17</sup>

Klotho is a transmembrane protein that is expressed in a variety of organs, but especially in the kidney. It is mostly found in the distal tubules of mammalian kidneys, such as a mouse, rat, and human kidneys, but it's also found in the proximal tubule and the inner medullary collecting duct.<sup>17</sup>

Klotho interacts with other CKD-MBD markers (parathyroid hormone, phosphate, fibroblast growth factor-23, and 1,25-[OH]2 vitamin D3) to play a key role in mineral homeostasis. klotho is the enzyme that transforms FGFR1(IIIc) into an aGF23-specific receptor. Furthermore, because of its capacity to increase phosphaturia and limit urine calcium loss, klotho is also known as a calciophosphoregulatory protein. Exogenous klotho treatment may attenuate or prevent the development of CKD-MBD, while deficiency leads to a constellation of disturbed mineral metabolism, secondary hyperparathyroidism, vascular calcification, and cardiac hypertrophy.<sup>18</sup>

### Calciprotein particles CPPs

Calciprotein particles (CPPs) are a type of calciprotein. CPPs are a Calcium, Phosphate and Fetuin-A complex that plays a key role in Hydroxyapatite delivery to bone. Their levels rise as P and Ca levels go up. As a result of CKD, atherosclerosis and vascular inflammation develop. In addition, CPPs rise in CKD stages I and II before the increase in FGF-23.<sup>19</sup>

### Hyperphosphatemia

By impairing skeletal function, CKD contributes to hyperphosphatemia and vascular calcification. Increased blood phosphorus levels are the result of increased phosphate released into the plasma and reduced phosphate deposition due to bone resorption.<sup>20</sup> Through an increased calcium-phosphorus product, hyperphosphatemia drives osteoblastic transition in the vasculature and directly leads to Mineralization outside the skeleton.<sup>21</sup>

Hyperphosphatemia has other key implications in the CKD-MBD axis. Hyperphosphatemia inhibits 1-alpha-hydroxylase activity in the kidney, which contributes to calcitriol insufficiency.<sup>22</sup> Hyperphosphatemia directly activates parathyroid cells in the parathyroid gland, regardless of calcium or calcitriol levels, resulting in nodular hyperplasia and increased PTH secretion.<sup>23</sup> Phosphorus promotes FGF23 secretion by osteocytes in the skeleton.<sup>24</sup>

### Calcium and vitamin D

As CKD progresses and the functional nephron mass diminishes, as well as hyperphosphatemia and increased FGF-23, 1a hydroxylase activity is suppressed, resulting in calcitriol shortage and decreased intestinal Calcium absorption.<sup>25</sup>

### Vascular calcification promoters

Phosphate is the VC promoter that has received the most attention. Traditional risk factors for VC include advanced age, hypertension, poor glycemic control, smoking, dyslipidemia, and others, while non-traditional risk factors include inflammation, oxidative stress, and CKD-MBD.<sup>26</sup>



## Calcium, phosphorus, and vitamin D

Calcium and Phosphate levels in human aortic cell cultures were shown to be higher in CKD patient's cell cultures. This greatly increased Ca-P nucleation causes calcification of the matrix vesicles of living smooth muscle cells as well as the exocytosis of dead cells. It's worth mentioning that calcification was prevented when these cells were exposed to non-uremic human serum containing bone morphogenetic proteins (BMPs) and fetuin-A.<sup>27</sup> Phosphate increases the expression of core-binding factor 1 (Cbfa1), which induces smooth muscle cell differentiation into osteoblasts, implying that other toxins, yet unknown, and hyperphosphatemia are linked to the upregulation of Cbfa1, resulting in increased expression of bone matrix in the vascular tissue, resulting in progressive calcification, particularly in patients on dialysis.<sup>28</sup>

## Parathormone and fibroblast growth factor-23

In persons with CKD, high levels of FGF-23 have been related to an increased risk of cardiovascular illness, as well as a higher rate of renal replacement failure and fatality. FGF-23 is a direct pathogenic agent producing LVH in humans, as well as a biomarker related to cardiovascular risk in CKD through stimulation of the calcineurin pathway in cardiac myocytes and activation of the calcineurin pathway in cardiac myocytes to promote Ca reabsorption. Klotho regulates the apical Ca entry channel in the renal distal tubules. Recent research has found that Klotho deficiency has been associated with CVD, including vascular stiffness, uremic vasculopathy, and "calciophylaxis."<sup>29</sup>

## Cardiovascular

The CKD-MBD raises hypertension, pulse wave velocity, and stroke volume mass in both the general population and those with CKD, all of which are surrogates for heart disease risk.<sup>30</sup> Early CKD is marked by structural and functional abnormalities of the vasculature, including vascular stiffness and endothelial dysfunction, which contribute to vascular calcification, a common aging process that is accelerated to the greatest extent seen in clinical practice in CKD. Arterial calcification increases vascular rigidity and promotes the development of LVH in both local and donor CKD patients, both of which increase heart disease risk and cardiovascular mortality.<sup>30</sup>

It is discovered that in animal models with mild renal insufficiency (equivalent to human stage 2 CKD), the synthesis of specific proteins in the contractile apparatus of aortic smooth muscle cells is reduced, indicating a dedifferentiated state of the vasculature in early Chronic Kidney Disease.<sup>31</sup>

## Clinical Manifestation

Metabolic bone disease is frequently asymptomatic in people with kidney disease, and symptoms do not develop until later in the illness's progression. Many of the symptoms are unclear, such as joint pain and stiffness, spontaneous tendon rupture, fracture tendency, and

proximal muscle spasms, fragile bone.<sup>32</sup>

## Diagnosis

Biochemical, radiological, and bone biopsy with subsequent pathological assessment are the main parameters utilized in routine CKD-MBD diagnosis.

## Biochemical parameters

Ca, P, alkaline phosphatase (ALP), and PTH screening, according to KDIGO criteria, is highly recommended.

At the early stages of CKD, "stage III" these measures should be consistently evaluated.<sup>33</sup> The total calcium level should be monitored regularly. However, serum Calcium not be used to diagnose CKD-MBD. Phosphate should be estimated with precautions. The Phosphate level varies during the day and after meals. As a result, fasting values should be checked.<sup>1</sup> Another bone marker is total ALP. An immunoassay for bone turnover is a good indicator of bone turnover, even if it isn't the greatest. Specific ALP is a superior marker, however, it is not often used.<sup>1</sup> It does not, however, provide additional information about bone turnover.<sup>34</sup>

High turnover disease, low turnover disease, and mixed uremic osteodystrophy were proposed by Sherald et al<sup>41</sup> in 1983, based on bone histomorphometry data.<sup>35</sup> The focus of this classification was on bone turnover; however, because bone biopsy is not commonly used to monitor patients, reliable biomarkers for screening and monitoring patients with CKD-MBD are needed. The KDIGO guidelines recommended that serum PTH be utilised in conjunction with total or bone-specific alkaline phosphatase (b-ALP) since high or low levels of these markers correspond to underlying bone turnover.<sup>36</sup> Bone mineral density (BMD) cannot predict the type of renal osteodystrophy in individuals with CKD G3a–G5 and CKD-MBD data.<sup>37</sup>

Measurements of blood PTH and ALP, or bone-specific ALP, can be used to evaluate bone disease in individuals with CKD G3a–G5 because substantially high or low values predict underlying bone disease.<sup>37</sup>

When conditions allow, bone-derived collagen metabolism indicators can be used in patients with CKD G3a–G5 can be used to determine the severity of a patient's bone disease.

## Biopsy of the bones

The gold standard for determining the pattern of bone disease is a bone biopsy, but it is not available everywhere and is invasive and time-consuming. There is a new classification system for bone histomorphometry known as turnover, mineralization, and volume in more current guidelines (TMV). Instead of using terminology like adynamic bone, mixed or moderate osteodystrophy, and high turnover bone disease (osteitis fibrosa), the TMV classification uses descriptors like T "low to high," M "normal to abnormal," and V "low to high".<sup>38</sup> In most patients with CKD, a bone biopsy is not contraindicated unless there are coagulation problems, soft tissue and/or skin inflammation, or a local infection over the iliac area.



The risk of problems after a bone biopsy is extremely minimal.<sup>39</sup>

### Radiological examinations

The regular radiological examinations used to diagnose CKD-MBD include the following.<sup>40</sup>

1. Imaging via X-ray to assess phalangeal tufts, subperiosteal bone degradation, linear osteosclerosis of the spine, and lucent regions of the long bones are among the usual radiological procedure followed in the diagnosis of CKD-MBD
2. Ultrasound examination (US) can help diagnose PTG hyperplasia and differentiate between diffuse and nodular hyperplasia.
3. 3. Other approaches for identifying CKD-MBD include computed tomography (CT) and magnetic resonance imaging (MRI) of the skeleton, however they are often insensitive.
4. Bone densitometry (DEXA scan) can be used, however, the results must be carefully interpreted because it cannot distinguish between osteoporosis and CKD-MBD.

### Management

Correction of hyperphosphatemia, hypocalcemia, and maintaining an adequate calcitriol concentration are the cornerstones of CKD-MBD treatment. Mineral problems, unfortunately, remain difficult to control even with enhanced PTH synthesis and secretion.<sup>41</sup>

The goal of CKD-MBD management is to avoid secondary hyperparathyroidism's negative implications. As a result, secondary hyperthyroidism treatment is dependent on well-established measurable surrogate markers of mineral bone disease.<sup>42</sup> Serum calcium, phosphate, 25-hydroxyvitamin and intact parathyroid hormone are markers. Thus, treatment should be based on the current KDIGO guidelines on serial trends of these biochemical markers.<sup>43</sup>

Even though hyperphosphatemia has been associated with severe negative clinical outcomes, no evidence lowering phosphate levels improves patient outcomes. A recent randomized clinical trial, for example, found a non-significant drop in serum phosphate and a significant fall in serum phosphate, FGF23 levels in the blood are dropping, and the condition is getting worse in Scores of coronary calcification in patients who received phosphate-lowering medication.<sup>44</sup> As a result, the new KDIGO recommendation that hyperphosphatemia prevention is more important than treatment or normalization of phosphate levels in patients with CKD stages G3a to G5D.<sup>43</sup>

Phosphate restriction in the diet, phosphate-lowering medications, and dialysis for individuals with CKD stage G5D are all options for preventing hyperphosphatemia.

### Phosphate restriction

Phosphate intake should be limited to less than 800 mg per day, which can be accomplished by restricting the intake of high-phosphate-containing sodas and fizzy drinks with phosphate additions. However, because the vast majority of phosphate-rich foods are also high in protein, these individuals' health should be closely monitored to avoid deterioration.<sup>45</sup>

When developing dietary recommendations, keep phosphate as a source in mind. This is critical since the gastrointestinal absorptive limit for various phosphate sources has varied. Inorganic phosphate, such as that found in added foods and beverages, has a gastrointestinal absorption rate of between 80 and 100 percent, but plant-based phosphate, such as that found in nuts, has a rate of between 20 and 40 percent.<sup>45</sup>

Phosphate binders are frequently given with meals to prevent phosphate from being absorbed from the gut by generating a nonabsorbable complex with the phosphate.<sup>46</sup> Aluminum-based phosphate binders, Ca-based phosphate binders, and non-Ca-based phosphate binders are the three types of phosphate binders available.<sup>45</sup>

Aluminum-based phosphate binders have been limited in their long-term use due to side effects such as osteomalacia and encephalopathy.<sup>47</sup> The usage of calcium-containing phosphate binders versus noncalcium-containing phosphate binders should be guided by the patients' calcium and PTH serum levels. Overuse of calcium-based phosphate binders has been associated with negative consequences, especially in non-dialysis patients.<sup>44</sup>

### Management of hyperphosphatemia

Patients with hyperphosphatemia must take calcium-based P binders, however, hypercalcemia is a risk. As a result, managing with a non-Ca-based P binder, such as Sevelamer carbonate, a non-Ca-based P binder, is critical, with the potential to lower low-density lipoprotein cholesterol levels. Lanthanum carbonate is a good P binder as well, although it's still hard to come by in many areas. At each meal, P binders should be taken. CKD patients' poor adherence is caused in part by a high tablet burden.<sup>46</sup> It is suggested that you limit your P intake to less than 1000 mg per day. Soft drinks, fast and processed foods, and Coca-Cola should all be avoided. The majority of patients, especially those on dialysis, find that dietary restriction is insufficient. Dialysis adequacy is useful in lowering phosphate levels, but more frequent dialysis, such as short daily, long nocturnal HD is much more important.<sup>1</sup>

### Phosphate removal through dialysis

Dialysis removes phosphate depending on the type of dialysis, the length of the session, and the dialysate used.

An estimated 2.3–2.6 g of phosphate will be eliminated each week if dialysis sessions are 4 hours long and



performed three times per week. Phosphate elimination rises to 3.0–3.6 g per week when the session length is increased to 8 hours three times per week (as in nocturnal dialysis). Peritoneal dialysis patients will have an estimated 2.0–2.2 g of phosphate removed per week, with 4 L exchanges each day.<sup>45,48</sup>

### Management of altered calcium

There are various advantages to combining calcium acetate and magnesium carbonate. Magnesium has been shown to lessen the risk of calcification in soft tissues.<sup>1</sup> Bisphosphonates are a type of medication used to treat osteoporosis and malignant bone disease. Because they are exclusively excreted by the kidneys, they are contraindicated in severe renal insufficiency. Bisphosphonates have been shown in animal trials to prevent HPT bone alterations. Dialyzable substances include Clodronate, Pamidronate, and Ibandronate.<sup>49</sup>

### Management of altered vitamin D level

In CKD patients, vitamin D or vitamin D analogs are frequently used to prevent and treat SHPT. Calcitriol was the most widely used agent for many years. Paricalcitol, a vitamin D analog also known as selective VDR activator, is now more commonly used.<sup>50</sup>

### Management of secondary hyperparathyroidism

Traditional treatment of SHPT in patients with CKD, according to the new KDIGO guidelines, is limited to the administration of the vitamin D analog calcitriol or dietary P binders to reset Ca, P, and PTH levels.<sup>4</sup>

However, because vitamin D analog treatment raises blood Ca and P levels, effective HPT therapies that effectively control PTH levels without causing hypercalcemia are required. Calcitriol, paricalcitol, and doxercalciferol are the most frequent vitamin D medications used to treat secondary hyperparathyroidism.

### Cinacalcet

It is a calcimimetic that lowers PTH levels immediately after treatment by raising the sensitivity of the calcium-sensing receptor to extracellular calcium ions.

Dose: Dose of 30 mg and increased based on response;

Route of Administration: parenteral

Frequency: cinacalcet (Etelcalcetide) is given three times weekly after dialysis.

**Side Effect:** hypocalcemia, it's important to monitor serum calcium and phosphate levels frequently.<sup>51</sup>

### Calcitriol

It is a vitamin D receptor activator (VDRA) that suppresses PTH when taken daily or three times weekly. However, because vitamin D receptors are widely available, they can be used in a variety of ways.

The administration of calcitriol also improves the function

of parathyroid tissues, Calcium and phosphorus absorption from the intestines

Side Effects: hypercalcemia, increase phosphate levels.

### Paricalcitol

A more receptor-selective injectable paricalcitol was developed to treat the hypercalcemia and hyperphosphatemia associated with oral calcitriol it was made available in 1998.

The suggested beginning dose for parenteral paricalcitol is 2–5 g per dialysis session, which should be gradually reduced to 1–2 g every dialysis session if your PTH level is less than 100 pg/mL, you should discontinue the VDR's.

Thus, calcimimetic, calcitriol, or vitamin D analogs are all regarded first-line alternatives for reducing PTH in CKD stage 5D, with serum calcium, phosphate, and PTH levels guiding the choice of which agent to use.<sup>52</sup> Finally, while parathyroidectomy is recommended for patients with secondary hyperparathyroidism who have failed to respond to medical treatment, the best option is between subtotal parathyroidectomy (subtotal PTX) and total parathyroidectomy with auto-transplantation (total PTX-AT) has not been determined. Both surgical procedures have been proven to be effective and produce similar results.<sup>18</sup>

### Hormone replacement therapy

In addition to ROD, postmenopausal dialysis patients may develop osteoporosis. Due to the pharmacokinetics of estradiol in renal failure, hormone replacement therapy (HRT) could have both positive and negative consequences, especially in uremic women. In non-uremic women, therapeutic alternatives such as selective estrogen receptor modulators (SERMs) have demonstrated the benefits of estrogen on bone and serum cholesterol levels while avoiding its negative effects on the breast and endometrial. In postmenopausal uremic women, Raloxifene and other SERMs may thus be a useful alternative to HRT.<sup>52</sup>

### Teriparatide

Osteoporosis is treated with an anabolic drug, a PTH analog Teriparatide helped improve BMD and reduce the incidence of fractures in patients with mild to moderate CKD who had normal serum PTH. The use of teriparatide in CKD, a condition linked to HPT, appears to be unsuitable because higher PTH levels are a contraindication to the medicine. Teriparatide may be beneficial in CKD patients with adynamic bone disease and those who have had their parathyroid glands removed before.<sup>53</sup>

### Denosumab

Denosumab, a RANK-L antagonist, is a powerful anti-resorptive drug. It is a monoclonal antibody that inhibits osteoclast proliferation and growth by binding to the receptor activator of the NFkB ligand. Denosumab, unlike bisphosphonates, is not cleared by the kidney, hence there



is no concern of over suppression of bone turnover due to drug buildup in patients with CKD.<sup>4</sup>

### Strontium ranelate

This medicine restores bone remodeling while reducing the risk of hypocalcemia and adynamic bone disease by balancing bone remodeling without inhibiting bone resorption. Strontium is contraindicated in patients with a GFR of less than 30 ml/min, i.e. CKD stages IV and V, due to renal excretion.<sup>4</sup>

### CONCLUSION

Bone mineral density is a major concern in chronic renal disease patients and renal osteodystrophy must be ruled out early for better treatment outcomes. Regular testing of phosphate, calcium, parathyroid, vitamin D levels must be done in CKD patients to prevent further complications. Biochemical, radiological, and bone biopsy with subsequent pathological assessment are the main parameters utilized in routine CKD-MBD diagnosis. The treatment include correction of altered phosphate, calcium, PTH, vitamin D levels. Other treatment options include hormonal replacement therapy, teriparatide, denosumab, strontium ranelate. However, treatment of CKD-MBD is still a major challenge and hence, further research studies must be performed.

### Abbreviations

AER- albumin excretion rate; ACR- albumin-to-creatinine ratio; CKD- chronic kidney disease, FGF-Fibroblast Growth Factor; HPT- hyperparathyroidism; GFR- glomerular filtration report

### REFERENCES

- Pavlovic D, katicic D, Gulin T, et al. chronic kidney disease mineral bone disorder. *Periodicum Biologorum* 2015; 117: 81-85.
- Fukagawa M and Komaba H. Chronic kidney disease-mineral and bone disorder in Asia. *Kidney Diseases* 2017; 3: 1-7.
- Singh S, Grabner A, Yanucil C, Schramm K, Czaya B, Krick S, Czaja MJ, Bartz R, Abraham R, Di Marco GS, Brand M, Wolf M, Faul C. Fibroblast growth factor 23 directly targets hepatocytes to promote inflammation in chronic kidney disease. *Kidney Int.* 2016 Nov;90(5):985-996. doi: 10.1016/j.kint.2016.05.019. Epub 2016 Jul 22. PMID: 27457912; PMCID: PMC5065745.
- Osama Mosbah. Chronic Kidney Disease-Mineral and Bone Disorders (CKD-MBD). *Archives of Nephrology and Urology* 2019; 2: 033-051
- Eknoyan G, Lameire N, Barsoum R, Eckardt KU, Levin A, Levin N, Locatelli F, MacLeod A, Vanholder R, Walker R, Wang H. The burden of kidney disease: improving global outcomes. *Kidney Int.* 2004 Oct; 66(4): 1310-4. doi: 10.1111/j.1523-1755.2004.00894.x. PMID: 15458424.
- Delanaye P, Souberbielle JC, Lafage-Proust MH, Jean G, Cavalier E. Can we use circulating biomarkers to monitor bone turnover in CKD hemodialysis patients? Hypotheses and facts. *Nephrol Dial Transplant.* 2014 May;29(5):997-1004. DOI: 10.1093/ndt/gft275. Epub 2013 Jul 17; PMID: 23868144.
- Gal-Moscovici A, Sprague SM. Bone health in chronic kidney disease-mineral and bone disease. *Adv Chronic Kidney Dis.* 2007 Jan; 14(1): 27-36. doi: 10.1053/j.ackd.2006.10.010. PMID: 17200041.
- Moe S, Drüeke T, Cunningham J, Goodman W, Martin K, Olgaard K, Ott S, Sprague S, Lameire N, Eknoyan G; Kidney Disease: Improving Global Outcomes (KDIGO). Definition, evaluation, and classification of renal osteodystrophy: a position statement from Kidney Disease: Improving Global Outcomes (KDIGO). *Kidney Int.* 2006 Jun; 69(11): 1945-53. doi: 10.1038/sj.ki.5000414. PMID: 16641930.
- Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. *Kidney inter., Suppl.* 2013; 3: 1–150.
- Pulskens, Wilco & Verkaik, Melissa & Sheedfar, Fareeba & Loon, Ellen & Sluis, Bart & Vervloet, Marc & Hoenderop, Joost & Bindels, René. (2015). Deregulated Renal Calcium and Phosphate Transport during Experimental Kidney Failure. *PLOS ONE.* 10. e0142510. 10.1371/journal.pone.0142510.
- Miyamoto K, Ito M, Kuwahata M, Kato S, Segawa H. Inhibition of intestinal sodium-dependent inorganic phosphate transport by fibroblast growth factor 23. *Ther Apher Dial.* 2005 Aug; 9(4): 331-5. doi: 10.1111/j.1744-9987.2005.00292.x. PMID: 16076377.
- Pateinakis, Panagiotis & Papagianni, A. (2013). Fibroblast growth factor-23 and adverse clinical outcomes in chronic kidney disease patients. *OA Nephrology.* 1. 10.13172/2053-0293-1-1-481.
- Shimada T, Hasegawa H, Yamazaki Y, Muto T, Hino R, Takeuchi Y, Fujita T, Nakahara K, Fukumoto S, Yamashita T. FGF-23 is a potent regulator of vitamin D metabolism and phosphate homeostasis. *J Bone Miner Res.* 2004 Mar; 19(3): 429-35. doi: 10.1359/JBMR.0301264. Epub 2003 Dec 29. PMID: 15040831.
- Lewis R. Mineral and bone disorders in chronic kidney disease: new insights into mechanism and management. *Ann Clin Biochem.* 2012 Sep; 49(Pt 5): 432-40. doi: 10.1258/acb.2012.012004. Epub 2012 Jul 17. PMID: 22807503.
- Kuro-o, Makoto & Matsumura, Yutaka & Aizawa, Hiroki & Kawaguchi, Hiroshi & Suga, Tatsuo & Utsugi, Toshihiro & Ohyama, Yoshio & Kurabayashi, Masahiko & Kaname, Tadashi & Kume, Eisuke & Iwasaki, Hitoshi & Iida, Akihiro & Shiraki-Iida, Takako & Nishikawa, Satoshi & Nagai, Ryojo & Nabeshima, Yo-ichi. (1997). Mutation of the mouse Klotho gene leads to a syndrome resembling ageing. *Nature.* 390. 45-51. 10.1038/36285.
- Sitara D, Razzaque MS, Hesse M, Yoganathan S, Taguchi T, Erben RG, Jüppner H, Lanske B. Homozygous ablation of fibroblast growth factor-23 results in hyperphosphatemia and impaired skeletogenesis, and reverses hypophosphatemia in PheX-deficient mice. *Matrix Biol.* 2004 Nov; 23(7): 421-32. doi: 10.1016/j.matbio.2004.09.007. PMID: 15579309; PMCID: PMC2894977.



17. Waziri B, Duarte R, Naicker S. Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD): Current Perspectives. *Int J Nephrol Renovasc Dis.* 2019 Dec 24; 12: 263-276. doi: 10.2147/IJNRD.S191156. PMID: 31920363; PMCID: PMC6935280.
18. Akiyama K, Kimura T, Shiizaki K. Biological and Clinical Effects of Calciprotein Particles on Chronic Kidney Disease-Mineral and Bone Disorder. *Int J Endocrinol.* 2018 Mar 27; 2018: 5282389. doi: 10.1155/2018/5282389. PMID: 29780418; PMCID: PMC5892265.
19. Davies MR, Lund RJ, Mathew S, Hruska KA. Low turnover osteodystrophy and vascular calcification are amenable to skeletal anabolism in an animal model of chronic kidney disease and the metabolic syndrome. *J Am Soc Nephrol.* 2005 Apr; 16(4): 917-28. doi: 10.1681/ASN.2004100835. Epub 2005 Mar 2. PMID: 15743994.
20. Mathew S, Tustison KS, Sugatani T, Chaudhary LR, Rifas L, Hruska KA. The mechanism of phosphorus as a cardiovascular risk factor in CKD. *J Am Soc Nephrol.* 2008 Jun; 19(6): 1092-105. doi: 10.1681/ASN.2007070760. Epub 2008 Apr 16. PMID: 18417722; PMCID: PMC2396927.
21. Hruska KA, Mathew S, Lund R, Qiu P, Pratt R. Hyperphosphatemia of chronic kidney disease. *Kidney Int.* 2008 Jul; 74(2): 148-57. doi: 10.1038/ki.2008.130. Epub 2008 Apr 30. PMID: 18449174; PMCID: PMC2735026.
22. Moallem E, Kilav R, Silver J, Naveh-Many T. RNA-Protein binding and post-transcriptional regulation of parathyroid hormone gene expression by calcium and phosphate. *J Biol Chem.* 1998 Feb 27; 273(9): 5253-9. doi: 10.1074/jbc.273.9.5253. PMID: 9478982.
23. Larsson T, Nisbeth U, Ljunggren O, Jüppner H, Jonsson KB. Circulating concentration of FGF-23 increases as renal function declines in patients with chronic kidney disease, but does not change in response to variation in phosphate intake in healthy volunteers. *Kidney Int.* 2003 Dec; 64(6): 2272-9. doi: 10.1046/j.1523-1755.2003.00328.x. PMID: 14633152.
24. Malluche HH, Porter DS, Pienkowski D. Evaluating bone quality in patients with chronic kidney disease. *Nat Rev Nephrol.* 2013; 9(11): 671-680. doi:10.1038/nrneph.2013.198
25. Peres LA, Pércio PP. Mineral and bone disorder and vascular calcification in patients with chronic kidney disease. *J Bras Nefrol.* 2014 Apr-Jun; 36(2): 201-7. English, Portuguese. doi: 10.5935/0101-2800.20140031. PMID: 25055361.
26. Reynolds JL, Joannides AJ, Skepper JN, McNair R, Schurgers LJ, Proudfoot D, Jahnen-Dechent W, Weissberg PL, Shanahan CM. Human vascular smooth muscle cells undergo vesicle-mediated calcification in response to changes in extracellular calcium and phosphate concentrations: a potential mechanism for accelerated vascular calcification in ESRD. *J Am Soc Nephrol.* 2004 Nov; 15(11): 2857-67. doi: 10.1097/01.ASN.0000141960.01035.28. PMID: 15504939.
27. Jono S, McKee MD, Murry CE, Shioi A, Nishizawa Y, Mori K, Morii H, Giachelli CM. Phosphate regulation of vascular smooth muscle cell calcification. *Circ Res.* 2000 Sep 29; 87(7): E10-7. doi: 10.1161/01.res.87.7.e10. PMID: 11009570.
28. Hruska KA, Sugatani T, Agapova O, Fang Y. The chronic kidney disease - Mineral bone disorder (CKD-MBD): Advances in pathophysiology. *Bone.* 2017; 100: 80-86. doi:10.1016/j.bone.2017.01.023
29. Ix JH, Katz R, De Boer IH, Kestenbaum BR, Allison MA, Siscovick DS, Newman AB, Sarnak MJ, Shlipak MG, Criqui MH. Association of chronic kidney disease with the spectrum of ankle brachial index the CHS (Cardiovascular Health Study). *J Am Coll Cardiol.* 2009 Sep 22; 54(13): 1176-84. doi: 10.1016/j.jacc.2009.06.017. PMID: 19761940; PMCID: PMC2799242.
30. Fang Y, Ginsberg C, Seifert M, Agapova O, Sugatani T, Register TC, Freedman BI, Monier-Faugere MC, Malluche H, Hruska KA. CKD-induced wingless/integration1 inhibitors and phosphorus cause the CKD-mineral and bone disorder. *J Am Soc Nephrol.* 2014 Aug; 25(8): 1760-73. doi: 10.1681/ASN.2013080818. Epub 2014 Feb 27. PMID: 24578135; PMCID: PMC4116062.
31. Martin KJ, González EA. Metabolic bone disease in chronic kidney disease. *J Am Soc Nephrol.* 2007 Mar; 18(3): 875-85. doi: 10.1681/ASN.2006070771. Epub 2007 Jan 24. PMID: 17251386.
32. Chen W, Bushinsky DA. Chronic kidney disease: KDIGO CKD-MBD guideline update: evolution in the face of uncertainty. *Nat Rev Nephrol.* 2017 Oct; 13(10): 600-602. doi: 10.1038/nrneph.2017.118. Epub 2017 Aug 21. PMID: 28824172.
33. El-Husseini A, Sawaya BP. What is the role of bone biopsy in the management of adult dialysis patients? *Semin Dial.* 2014 May-Jun; 27(3): 266-9. doi: 10.1111/sdi.12236. Epub 2014 Mar 31. PMID: 24684712.
34. Sherrard DJ, Hercz G, Pei Y, Maloney NA, Greenwood C, Manuel A, Saiphoo C, Fenton SS, Segre GV. The spectrum of bone disease in end-stage renal failure--an evolving disorder. *Kidney Int.* 1993 Feb; 43(2): 436-42. doi: 10.1038/ki.1993.64. PMID: 8441240.
35. Sprague SM, Bellorin-Font E, Jorgetti V, Carvalho AB, Malluche HH, Ferreira A, D'Haese PC, Drüeke TB, Du H, Manley T, Rojas E, Moe SM. Diagnostic Accuracy of Bone Turnover Markers and Bone Histology in Patients With CKD Treated by Dialysis. *Am J Kidney Dis.* 2016 Apr; 67(4): 559-66. doi: 10.1053/j.ajkd.2015.06.023. Epub 2015 Aug 25. PMID: 26321176.
36. Liu ZH, Li G, Zhang L, Chen J, Chen X, Zhao J, Liang X. Executive Summary: Clinical Practice Guideline of Chronic Kidney Disease - Mineral and Bone Disorder (CKD-MBD) in China. *Kidney Dis (Basel).* 2019 Oct; 5(4): 197-203. doi: 10.1159/000500053. Epub 2019 Jul 9. PMID: 31768376; PMCID: PMC6873094.
37. Dousdampanis P, Trigka K. The importance of bone biopsy in chronic kidney disease-Mineral bone disorders. *Saudi J Kidney Dis Transpl.* 2017 Sep-Oct; 28(5): 992-996. doi: 10.4103/1319-2442.215150. PMID: 28937054.
38. Trueba D, Sawaya BP, Mawad H, Malluche HH. Bone biopsy: indications, techniques, and complications. *Semin Dial.* 2003 Jul-Aug; 16(4): 341-5. doi: 10.1046/j.1525-139x.2003.160631.x. PMID: 12926408.
39. Heymann E, Jenkins M and Goldsmith D. Clinical features and manifestations of CKD-MBD. *Clinical Reviews in Bone*





- and mineral Metabolism 2012;10:142-148.
40. Fukagawa M, Yokoyama K, Koiwa F, Taniguchi M, Shoji T, Kazama JJ, Komaba H, Ando R, Kakuta T, Fujii H, Nakayama M, Shibagaki Y, Fukumoto S, Fujii N, Hattori M, Ashida A, Iseki K, Shigematsu T, Tsukamoto Y, Tsubakihara Y, Tomo T, Hirakata H, Akizawa T; CKD-MBD Guideline Working Group; Japanese Society for Dialysis Therapy. Clinical practice guideline for the management of chronic kidney disease-mineral and bone disorder. *Ther Apher Dial.* 2013 Jun; 17(3): 247-88. doi: 10.1111/1744-9987.12058. PMID: 23735142.
  41. Tomasello, S. Secondary Hyperparathyroidism and Chronic Kidney Disease. *Diabetes Spectrum.* 2008;21:19-25. 10.2337/diaspect.21.1.19.
  42. Ketteler M, Block GA, Evenepoel P, Fukagawa M, Herzog CA, McCann L, Moe SM, Shroff R, Tonelli MA, Toussaint ND, Vervloet MG, Leonard MB. Executive summary of the 2017 KDIGO Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD) Guideline Update: what's changed and why it matters. *Kidney Int.* 2017 Jul; 92(1): 26-36. doi: 10.1016/j.kint.2017.04.006. Erratum in: *Kidney Int.* 2017 Dec;92(6):1558. PMID: 28646995.
  43. Block GA, Wheeler DC, Persky MS, Kestenbaum B, Ketteler M, Spiegel DM, Allison MA, Asplin J, Smits G, Hoofnagle AN, Kooienga L, Thadhani R, Mannstadt M, Wolf M, Chertow GM. Effects of phosphate binders in moderate CKD. *J Am Soc Nephrol.* 2012 Aug; 23(8): 1407-15. doi: 10.1681/ASN.2012030223. Epub 2012 Jul 19. PMID: 22822075; PMCID: PMC3402292.
  44. Hwang E, Choi BS, Oh KH, Kwon YJ, Kim GH. Management of chronic kidney disease-mineral and bone disorder: Korean working group recommendations. *Kidney Res Clin Pract.* 2015 Mar; 34(1): 4-12. doi: 10.1016/j.krcp.2015.02.002. Epub 2015 Feb 24. PMID: 26484013; PMCID: PMC4570602.
  45. Luyera J, Scialla JJ. Update on Chronic Kidney Disease Mineral and Bone Disorder in Cardiovascular Disease. *Semin Nephrol.* 2018 Nov; 38(6): 542-558. doi: 10.1016/j.semnephrol.2018.08.001. PMID: 30413250; PMCID: PMC6372293.
  46. Alfrey AC. Aluminum toxicity in patients with chronic renal failure. *Ther Drug Monit.* 1993 Dec; 15(6):593-7. doi: 10.1097/00007691-199312000-00025. PMID: 8122300.
  47. Cupisti A, Gallieni M, Rizzo MA, Caria S, Meola M, Bolasco P. Phosphate control in dialysis. *Int J Nephrol Renovasc Dis.* 2013 Oct 4; 6:193-205. doi: 10.2147/IJNRD.S35632. PMID: 24133374; PMCID: PMC3797240.
  48. Bergner R. Bisphosphonate therapy in renal osteodystrophy--a review. *J Nephrol.* 2013 May-Jun; 26(3): 450-5. doi: 10.5301/jn.5000188. Epub 2012 Jul 2. PMID: 22760876.
  49. Cunningham J, Locatelli F, Rodriguez M. Secondary hyperparathyroidism: pathogenesis, disease progression, and therapeutic options. *Clin J Am Soc Nephrol.* 2011 Apr; 6(4): 913-21. doi: 10.2215/CJN.06040710. Epub 2011 Mar 31. PMID: 21454719.
  50. Weisinger JR, Heilberg IP, Hernández E, Carlini R, Bellorin-Font E. Selective estrogen receptor modulators in chronic renal failure. *Kidney Int Suppl.* 2003 Jun; (85): S62-5. doi: 10.1046/j.1523-1755.63.s85.15.x. PMID: 12753268.
  51. Lima GA, Paranhos Neto Fde P, Pereira GR, Gomes CP, Farias ML. Osteoporosis management in patient with renal function impairment. *Arq Bras Endocrinol Metabol.* 2014 Jul; 58(5): 530-9. doi: 10.1590/0004-2730000003360. PMID: 25166044.

**Source of Support:** The author(s) received no financial support for the research, authorship, and/or publication of this article.

**Conflict of Interest:** The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

For any question relates to this article, please reach us at: [globalresearchonline@rediffmail.com](mailto:globalresearchonline@rediffmail.com)  
 New manuscripts for publication can be submitted at: [submit@globalresearchonline.net](http://submit@globalresearchonline.net) and [submit\\_ijpsrr@rediffmail.com](mailto:submit_ijpsrr@rediffmail.com)