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Management of Osteoporosis in Chronic Kidney Diseases

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1. Introduction

1.1. Chronic kidney disease (CKD)

Chronic kidney disease (CKD) is an international public health problem affecting 5–10% of the world population, as it is responsible for high morbidity and mortality particularly affecting population over 60 years of age. [1]. CKD is defined as abnormal renal function or structure [1].

GFR category	GFR (ml/min/1.73 m ²)	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
G4	15–29	Severely decreased
G5	<15	Kidney failure

* Relative to young adult level

Abbreviations: CKD, chronic kidney disease; GFR, glomerular filtration rate

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Table 1. Stages in CKD

As classified by National Kidney Foundation [1] and Kidney disease improving global outcome (KDIGO) [2] CKD has 5 stages based on e GFR (estimated glomerular filtration rate) (Table 1) and markers of kidney damage. CKD is diagnosed when e GFR is consistently $<60\text{ml}/\text{min}/1.73^2$ on at least two separate occasion separated by a period of more than 3 months. Stage 3 is further sub classified into 3a (45 to 59ml/min) and 3b (30 to 44ml/min) and includes albuminuria in the classification. $\text{eGFR} \geq 30\text{-}60\text{ml}/\text{min}/1.73^2$ or stage 3 is referred as “early CKD” and $\text{eGFR} < 30$ or stage 4-5 is referred as “late CKD”. Stage 5 or e GFR < 15 is also referred as end stage renal disease (ESRD).

1.2. Bone mineral disruption in CKD

As kidney function declines, there is a progressive deterioration in mineral homeostasis, with a disruption of normal serum concentrations of calcium and phosphorus. The disturbance in mineral homeostasis is due to changes in circulating levels of hormones such as parathyroid hormone (PTH), 25-hydroxyvitamin D [25 (OH) D], 1,25-dihydroxyvitamin D [1,25 (OH) D] or calcitriol and fibroblast growth factor (FGF-23) [3].

Beginning in CKD stage 3 or early CKD, the ability of the kidney to appropriately excrete a phosphate load is diminished. However, serum calcium and phosphorous levels remain within the reference range with PTH either within the reference range or slightly elevated. Rise in FGF-23 appears much earlier than changes in serum phosphate or PTH [4,5]. FGF-23 is produced by osteocytes and osteoblasts. It has phosphaturic action where by it reduces the renal tubular reabsorption of phosphate by reducing the expression of sodium phosphate cotransporters in renal tubule through Klotho-FGF receptor. Therefore, FGF-23 production is stimulated by impaired renal excretion of phosphate and elevated 1,25 (OH)D. FGF-23 indirectly stimulates PTH secretion by decreasing the synthesis of 1,25 (OH)D. Studies have shown the effect of this raised FGF-23 on mortality in dialysis patients [6].

As CKD progresses further, hyperphosphatemia stimulates the secretion of PTH, leading to secondary hyperparathyroidism. Additionally, hyperphosphatemia itself has direct posttranslational effect on PTH synthesis [7]. Further deterioration in kidney function results in impaired conversion of 25 (OH) D to 1,25 (OH) D, reducing 1,25 (OH)D synthesis. This reduces intestinal calcium absorption and ensuing hypocalcaemia further stimulates PTH secretion aggravating secondary hyperparathyroidism. FGF-23 also down regulates the synthesis of 1,25 (OH)D through 1- α hydroxylase, which exacerbates the secondary hyperparathyroidism. In addition, there is evidence at the tissue level of a down regulation of vitamin D receptor and of resistance to the actions of PTH. Due to target tissue resistance to PTH action, kidney fails to respond adequately to PTH, aggravating secondary hyperparathyroidism.

Thus there is continuous secretion of PTH due to hyperphosphatemia, hypocalcaemia, reduced synthesis of 1,25 (OH)D resulting in parathyroid hyperplasia [8]. This is commonly seen in late CKD, which presents with mineral and hormonal disturbances such as hypocalcaemia, hyperphosphatemia, raised PTH, raised FGF-23 and low vitamin D status.

The disruption in mineral and endocrine functions in CKD has significant effect on bone remodeling as secondary hyperparathyroidism stimulates the bone resorption. Vitamin D deficiency disrupts mineralization of bone leading to overall deterioration in bone quality. Hence a wide spectrum of bone metabolic disorders is seen in patients with CKD stage 3-5 and those on dialysis (stage 5D). This mineral and hormonal disruption in CKD alters the bone morphology and constitutes renal osteodystrophy of CKD. PTH and vitamin D are the major hormones, which, are involved in renal osteodystrophy. Besides this recent studies have shown that FGF-23 also contributes to vitamin D deficiency [10]. More recently, there has been an increasing concern for extra skeletal calcification that may result from the deranged mineral and bone metabolism of CKD. Extra skeletal calcification or vascular calcifications is major risk for cardiovascular disease in CKD patients contributing to high morbidity and mortality in this sub population group.

1.3. Bone metabolic disorders in CKD

CKD can present with wide spectrum of bone metabolic disorders, including renal osteodystrophy and osteoporosis. The manifestation of bone metabolic disorders is influenced by the severity of CKD. Osteoporosis is predominant in early CKD where it is potentiated by risk factors such as ageing, gender (post menopausal women), poor calcium and vitamin D intake, premature menopause, medications and chronic inflammatory disorders. These risk factors reduces the bone mass and results in osteoporosis. Renal osteodystrophy is predominant in late CKD where impaired bone and mineral homeostasis associated with hormonal disturbances affects the bone quality and mineralization. Both types of bone metabolic disorders increase the risk of bone fragility fractures thereby contributing to high morbidity and mortality in CKD patients.

1.3.1. Osteoporosis

Osteoporosis, which is characterized by low bone mass, is traditionally diagnosed as low bone mineral density (BMD). Osteoporosis as defined by WHO is the measurement of bone density at lumbar spine or hip which is equal to or less than 2.5 standard below the bone density of young adult reference population. DEXA or dual energy X ray absorptiometry is recommended as a diagnostic tool for measuring BMD. Osteoporosis is more common in postmenopausal women particularly Caucasian women [11]. Pathologically, osteoporosis is associated with high bone turnover due to increased osteoclastic activity, increasing the bone resorption.

Since osteoporosis disrupts bone quality, patients with osteoporosis are at increased risk of fractures. The BMD provides information on the likelihood of fracture risk in patients as lower is the BMD, higher is the risk of fracture and vice versa. Besides BMD, several factors identify the risk of fracture in an individual such as ageing, gender (post menopausal women), low body mass index, smoking, alcohol intake, parental history of hip fracture, previous fracture, steroid intake, rheumatoid arthritis and inflammatory bowel diseases. The risk of osteoporosis in general population is being assessed by fracture risk assessment tool (FRAX) provided by WHO [12].

Since osteoporosis is commonly seen in postmenopausal women or men above 50 years of age, this population group also has a high incidence of early CKD. Whereas patients with late CKD have renal osteodystrophy, which is characterized by abnormal bone quality with normal or high bone mineral content. Hence osteoporosis in CKD is most appropriate only for early CKD. Whereas in CKD 4-5 or 5D stages (late CKD), low BMD should be designated as having 'CKD with low BMD.' The prevalence of osteoporosis is high in early CKD whereas in late CKD it coexists with renal osteodystrophy.

1.3.2. CKD-MBD

KDIGO introduced a clear defined terminology for renal osteodystrophy in CKD patients, which is based on diagnostic tools [1]. The wide spectrum of bone metabolic disorders, which encompasses renal osteodystrophy is now defined as CKD associated mineral and bone disorder or CKD-MBD. This includes:

- Disruption in mineral homeostasis such as calcium, phosphorous
- Hormonal disturbances involving PTH, vitamin D and FGF-23
- Bone metabolic disorders characterized by high or low bone turnover affecting bone quality and strength
- Extra skeletal calcification (vascular or soft tissue) increasing the cardiovascular risk

Three types of bone metabolic disorders are seen in CKD-MBD as classified by bone histomorphometry:

- Osteitis fibrosa (OF): characterized by increased bone turnover and bone resorption due to secondary hyperparathyroidism
- Osteomalacia (OM): defective bone mineralization due to low vitamin D status
- Adynamic bone (ABD): reduced bone turnover characterized by reduced bone resorption and formation
- Mixed uremic osteodystrophy: characterized by mixed pattern of high and low bone turnover

CKD-MBD is usually seen in patients with late CKD (stages 4-5/D). As CKD progresses to stage 3, mild secondary hyperparathyroidism results in high bone turnover where bone resorption exceeds bone formation. Further progress into stage 4 results in severe secondary hyperparathyroidism with markedly increased bone turnover manifesting as marrow fibrosis with increased osteoid production and abnormal mineralization. Further vitamin D deficiency due to reduced vitamin D production or resistance to its action in stage 4 leads to defective mineralization of bone or osteomalacia. Besides this, vitamin D deficiency also reduces the bone formation and increases the osteoclast production [13]. Approximately 60% of CKD-MBD present with normal or low bone turnover whereas 40% present with high bone turnover.

Thus secondary hyperparathyroidism, which accompanies CKD, has a significant effect on the bone metabolism. Over the years, several approaches have been used to manage secondary hyperparathyroidism such as calcium salts to bind phosphate, vitamin D analogues to correct hypocalcaemia and vitamin D deficiency, parathyroidectomy in tertiary hyperparathyroidism to correct hypercalcaemia, calcimimetic drugs are used as an alternative to parathyroidectomy. All these therapies are given to reduce the effect of PTH on bone and therefore over-suppression of PTH over a prolonged time reduces the bone turnover and leads to adynamic bone disease (ABD) [14]. Studies have shown that 30% patients in CKD 4 and between 15 and 60% patients in CKD 5 or 5D has ABD [9]. ABD in CKD-MBD is characterized by subnormal osteoid tissue, mineralization, reduced osteoclast and osteoblast activity. Thus a large proportion of patients with CKD-MBD presents more frequently with ABD than OM or OF.

The prevalence of ABD has been increasing in CKD population. The exact mechanisms contributing to this type of bone disorders is largely unknown. Nevertheless, several factors are thought to be aggravating this type of low bone turnover renal osteodystrophy. Dialysis fluid containing aluminum is deposited in bone and can impair bone mineralization and reduce bone turnover. However aluminum is no longer used in dialysis now. ABD is commonly seen in patients with diabetic nephropathy than in non-diabetics. Iron load is also thought to contribute to ABD. Patients with ABD are also susceptible to develop hypercalcaemia. The risk of hypercalcaemia is exacerbated with administration of calcium carbonate in the CKD patients where it used as a phosphate binder. Patients with ABD have impaired ability to buffer calcium loads, a tendency to hypercalcaemia, as well as increased fracture rates and prevalence of extra-skeletal calcification.

1.3.3. Bone fragility fractures

Both osteoporosis and renal osteodystrophy in CKD-MBD can lead to increased bone fragility and fractures as both conditions are associated with low bone quality and poor bone micro-architecture. However both these diseases have different pathophysiological backgrounds. Bone fragility is due to varying combinations of low bone mineral content and abnormal bone quality. The fracture risk in CKD is magnified in elderly patients, women, diabetic, those using glucocorticoids, and in those with a longer exposure to dialysis. Patients in CKD are at higher risk of bone fragility fractures than those without CKD. FRAX (fracture risk assessment tool by WHO), which is used to estimate fracture risk in patients without CKD, is not applicable to patients with CKD as it will underestimate fracture risk.

The low impact fractures such as vertebral, non-vertebral and hip fractures are usually associated with osteoporosis as well as seen in CKD-MBD. The bone fragility fractures usually present with back pain leading to disability and death in these patients [15]. Hip fractures are common in CKD patients due to secondary hyperparathyroidism as PTH affects the cortical bone leading to high morbidity and mortality in these patients [16,17].

Patients with CKD-MBD have an increased risk of fracture compared with the general population, which can be due to osteomalacia, secondary hyperparathyroidism or adynamic

bone. In CKD-MBD secondary hyperparathyroidism potentiates the risk of bone fractures by increasing the bone turnover as seen in OF and OM. ABD is presumed to increase the risk of bone fractures due to impair ability of bone to repair micro fractures due to low bone turnover.

2. Management of osteoporosis in CKD

Since CKD involves wide spectrum of bone metabolic disorders, the identification of osteoporosis from other bone metabolic disorders is essential particularly in late CKD stage.

2.1. Investigations

2.1.1. Bone Mineral density (BMD)

Patients in early CKD are diagnosed by bone mineral density measured by DEXA scan. BMD measurement is indicated in early CKD provided they do not have manifestations of CKD-MBD. Since CKD-MBD encompasses a wide spectrum of bone metabolic dystrophy, which varies from renal osteodystrophy to osteoporosis, BMD measurement by DEXA is unable to differentiate between the types of bone metabolic disorders. More importantly there is no evidence that BMD in CKD-MBD predict the fracture risk in this subpopulation unlike in patients with early CKD. The risk of fractures is high in CKD-MBD as compared to early CKD as both renal osteodystrophy and osteoporosis increases the risk of fractures. Thus, the routine use of BMD in patients with late CKD has not been recommended. In patients with late CKD, the relationship between BMD and fractures is not as strong as that in the general population.

2.1.2. Biochemical markers

The biochemical markers are useful in assessing the bone metabolic status in CKD. These include:

- Hormones regulating the bone turnover
- Markers of bone collagen breakdown or formation
- Indicators of bone mineralization

The biochemical markers, help in differentiating the high bone turnover from low bone turnover particularly in CKD-MBD. Studies have shown that 40% CKD-MBD patients have high bone turnover compatible with OF and mixed bone disease where as 60% have low or normal bone turnover as seen in OM and AD.

Since these biochemical markers are non-specific they cannot help with the diagnosis of the type of bone metabolic disorder in CKD. They are helpful in monitoring the management of bone metabolic disorders in CKD patients.

- Hormones regulating the bone turnover

PTH regulates bone physiology. Serum PTH levels have been used as a surrogate indicator of bone turnover in the absence of bone biopsy. Raised PTH indicates vitamin D deficiency in early CKD where as late CKD it suggests high turnover bone metabolic disorders. PTH which is usually six times above the reference range, is associated with high bone turnover which can be seen in osteitis fibrosa cystica or osteomalacia but do not conclusively predict high turnover bone metabolic disease. The presence of low PTH (<15.9pmol/L or 150pg/ml) is consistent with low bone turnover osteodystrophy such as ABD. Thus raised PTH excludes the ABD in CKD-MBD.

- Biochemical markers of bone turnover

The markers of bone turnover help in the biochemical monitoring of bone metabolism. These markers include enzymes and proteins released during bone formation and degradation or resorption. The markers are not recommended for the diagnosis of osteoporosis. Nevertheless, they are useful in monitoring the treatment of osteoporosis in patients. The markers of bone turnover along with BMD are helpful in predicting the fracture risk in osteoporotic patients [18]. The markers are classified as formation markers, which are produced by osteoblasts or from pro collagen metabolism where as resorption markers are derived from degradation of osteoclasts or collagen tissue.

The markers of bone turnover includes:

a. Bone formation markers

1. Bone Alkaline phosphatase (BALP)
2. Type 1 N terminal procollagen peptide (P1NP)
3. Type 1 C-terminal procollagen peptide (P1CP)
4. Osteocalcin (OC)

b. Bone resorption markers

1. C terminal telopeptide (CTX)
2. N terminal telopeptide (NTX)
3. Pyridinolines (PYR)
4. Deoxypyridinolines (DPYR)
5. Tartrate resistant acid phosphatase (TRACP)

Role of bone turnover markers in early CKD

In patients with early CKD, markers of bone turnover predict the status of bone metabolism. The biochemical status of bone turnover is monitored by release of proteins and enzymes during bone formation and degradation products during bone resorption. The bone turnover markers are associated with bone loss and this is more significant with bone resorption than formation markers [19]. Large observational studies have shown that bone turnover markers

predict the fracture risk in osteoporotic patients and this is independent of BMD [20]. This relationship is again stronger for bone resorption than formation markers [21,22].

The bone turnover markers are not recommended for the diagnosis of osteoporosis as they have low specificity but high sensitivity in predicting the bone remodeling status. The bone turnover markers are recommended for the monitoring of therapy as they predict the response to treatment as early as 3-6 months of starting therapy. Therefore bone turnover markers predict the changes in bone remodeling status much earlier than BMD. IOF (International Osteoporosis Foundation) and IFCC (International Federation of clinical chemistry) has produced the recommendation for using bone turnover markers in fracture risk prediction and monitoring of osteoporosis.

Among markers of bone resorption, CTX in blood is commonly used for predicting the bone resorption status where as serum P1NP is used commonly as marker of bone formation. Urinary markers such as PYR, DPYR are not used routinely due to problems associated with urine collection and is influenced by creatinine excretion.

In early CKD raised bone turnover markers suggest the presence of bone metabolic disorders such as osteoporosis, pagets, osteomalacia, recent fracture or bone metastasis. Besides this rise in bone resorption markers in osteoporotic patients suggests:

- Risk of fractures
- Other bone metabolic diseases such as malignancy
- To initiate the treatment where BMD and clinical risk factors are not sufficient to make treatment decision

Osteoporotic patients on anti-resorptive therapy need repeat BMD every 2-3 years to assess the response to treatment. However, bone markers have the ability to assess the short-term response to anti-resorptive treatment every 6 months. Hence bone markers have a great value in monitoring anti-resorptive therapy in osteoporotic patients.

Among the markers of bone turnover, serum CTX or P1NP are preferred in monitoring the anti-resorptive treatment in osteoporotic patients with early CKD. The patients starting on anti-resorptive should have baseline serum CTX, treatment is monitored by evaluating the change in CTX at 6 months and reduction of >30% from baseline suggest efficacy and compliance to therapy [23].

Role of bone turnover markers in late CKD

Serum markers of bone remodeling can be useful to evaluate renal osteodystrophy in CKD-MBD. Most bone markers have renal metabolism and/or excretion and accumulate in renal failure. CTX, NTX, PYR and DPYR are influenced by renal function and its concentration in blood increases with deterioration in renal excretion. Among bone markers BALP, P1NP, P1CP and TRACP do not undergo renal metabolism or excretion and hence not influenced by renal functions.

The biochemical markers such as PTH and BALP are recommended for assessing the bone turnover in CKD-MBD. Further KDIGO does not suggest the use of markers of collagen

degradation such as CTX/NTX or PYR/DPYR in late CKD. BALP is preferred over cross linked telopeptides (CTX/NTX) as it is not excreted or metabolized by kidney, assess the rate of bone formation and increased levels exclude the ABD [24]. Nevertheless, BALP is a non-specific marker of high bone turnover as raised BALP reflects bone metabolic disorders such as vitamin D deficiency, secondary hyperparathyroidism and recent fracture. BALP has emerged as one of the most sensitive marker of bone turnover and correlates with bone histomorphometry and BMD. Studies have shown that BALP is a useful bone marker in the diagnosis of ABD and low BALP has a high sensitivity and specificity in excluding ABD as compared to PTH [25]. Similarly raised PTH also reflects the high bone turnover, which predicts OF, OM and excludes ABD. BALP is a better predictor of bone turnover than PTH. Hence normal bone ALP with normal or elevated PTH excludes high bone turnover in CKD-MBD. Studies have shown that BALP ≥ 20 U/L alone or with PTH ≥ 21 pmol/L has the highest sensitivity, specificity, positive and negative predictive value for the diagnosis of high bone turnover and excludes patients with normal or low bone turnover [26].

There is minimal data on the bone turnover markers in predicting fracture risk in CKD-MBD patients. Several studies have shown that PTH and BALP are better markers of bone turnover in CKD-MBD patients [25,27].

Based on evidence available, raised BALP with or without raised PTH excludes ABD in CKD-MBD patients. This has been further endorsed by KDIGO, which recommends the use of BALP and PTH in assessing the bone status in CKD-MBD patients [28].

Recommendations:

- i. Markers of bone turnover are non-specific markers of bone metabolism and therefore not to be used for the diagnosis of bone metabolic disorders in CKD.
- ii. Markers of bone turnover are used in monitoring the efficacy of therapy in CKD.
- iii. Serum CTX or P1NP are preferred makers for monitoring the therapy in osteoporotic patients in early CKD.
- iv. Since BALP is not excreted by kidney, it is a useful marker of bone turnover in CKD-MBD
- v. Low BALP indicates low bone turnover and ABD
- vi. BALP above the reference range excludes ABD
- vii. Besides BALP, TRACP is also not excreted by kidney and is a marker of increase bone resorption.
- viii. PINP which is a marker of bone formation and not affected by reduced e GFR has not been investigated in CKD-MBD
- ix. Bone resorption markers such as CTX are affected by reduced e GFR and thus not useful in evaluating the bone turnover status in CKD-MBD
- x. BALP and PTH together increases the predictive value of identifying ABD in CKD-MBD

- xi. Serum measurements of PTH and BALP are related to clinical outcomes, including relative risk of mortality. They also correlate with some of the bone histomorphometric measurements.
- xii. The biochemical markers of bone turnover are non-invasive and convenient to measure unlike bone biopsy and can be used to assess the bone status in CKD-MBD
 - Indicators of bone mineralization

The measurement of serum calcium, phosphorous and 25 (OH) vitamin D predict the status of bone mineralization in patients with CKD.

Serum calcium and phosphorous

The serum calcium is a poor predictor of total body calcium status as only 1% of calcium is extracellular and rest is in bone. The serum corrected calcium (after correcting serum calcium with albumin) is measured to assess the calcium status in clinical practice. Inorganic phosphorous plays a role in skeletal development. Serum phosphorous measures the inorganic phosphorous in blood. Both calcium and phosphorous are bound to hydroxyapatite crystals in bone, which helps with bone mineralization. Low serum calcium and phosphorous suggests vitamin D deficiency or secondary hyperparathyroidism. On the contrary, raised serum calcium or phosphorous in CKD patients suggest vitamin D over-replacement. The raised calcium and phosphorous in blood increases the risk of extra-skeletal calcification which further potentiates the cardiovascular risk in these patients. Thus monitoring of serum calcium and phosphorous is recommended in CKD patients particular in CKD-MBD patients.

Serum 25 (OH) vitamin D

Vitamin D deficiency is common in CKD patients due to impaired synthesis of active 1,25 (OH)D [29]. Low 25 (OH) vitamin D levels are seen in approximately 80% of patients with late CKD [26]. Studies have shown that 25 (OH) D has significant positive effect on PTH and BMD [30] as vitamin D deficiency aggravates the risk of secondary hyperparathyroidism, which further increases the bone resorption and bone metabolic disorders. Thus correction of vitamin D status has been recommended which will improve the bone mineralization. The serum 25 (OH) D above 75nmol/L levels is recommended in CKD patients that will reduce the risk of secondary hyperparathyroidism and improve bone mineralization.

Recommendations:

- 25 (OH)D to be measured in patients with CKD to assess the bone mineral status
- 25 (OH)D should be above 75nmol/L in CKD patients
- Serum corrected calcium and phosphorous should be within the reference range

2.1.3. Bone biopsy

CKD-MBD can lead to an abnormal bone quality even in the setting of a normal or high bone-mineral content. Bone biopsy provides measurements of bone turnover, mineralization, and volume. These help to assess bone quality and the underlying bone physiology. Bone biopsy

is a gold standard test for diagnosing the bone metabolic disorders in CKD-MBD. Nevertheless, it cannot be used in routine practice as it is a invasive procedure, painful to patient and can be carried out by an expert. Bone histomorphometry is studied by taking a biopsy from iliac crest of the bone. Since it is invasive procedure it cannot be carried routinely.

Recommendations:

- Bone biopsy is considered as the gold standard test for the diagnosis and classification of CKD-MBD.
- Not available routinely as it needs to be carried by a trained doctor.
- Bone biopsy is helpful if there is a history of unexplained bone pain or fracture in CKD-MBD patients to identify the type of bone metabolic disorder.

2.2. Treatment of bone metabolic disorders in CKD

Osteoporosis is a predominant bone metabolic disorder in early CKD where as its prevalence reduces in late CKD.

An osteoporotic patient in early CKD benefit with anti-resorptive treatment as it increases BMD and reduces fracture risk. Since CKD-MBD has wide spectrum of bone metabolic disorders, bisphosphonates may not be beneficial as seen in early CKD. The presence of ABD is a contraindication to bisphosphonates. In addition there is limited evidence regarding efficacy of treatments in reducing fracture risk in those patients with late CKD who have low BMD and biochemical abnormalities of CKD-MBD.

There are two types of therapies for treating osteoporosis in CKD: anti-resorptive which inhibits the osteoclastic induced bone resorption and anabolic therapy, which stimulates the osteoblastic induced bone formation.

Anti-resorptive is a first line therapy in the treatment of osteoporosis in postmenopausal women in whom it increases BMD both at cortical and trabecular site and reduces the fracture risk at vertebral, non-vertebral and hip.

Bisphosphonates (BP)

BP is the synthetic analogue of inorganic pyrophosphate, which inhibit the osteoclastic induced bone resorption and causes apoptosis of osteoclast. Thus BP reduces the bone turnover in osteoporosis. Alendronic acid is the commonly used BP and is recommended as first line therapy [31] for treating osteoporosis in post-menopausal women with osteoporosis. It has been shown to increase BMD and reduces the vertebral, non-vertebral and hip fractures. In early CKD patients with osteoporosis, BP is recommended as first line therapy. Recently continued use of BP in osteoporotic patients has been discouraged due to adverse affects associated with its long-term use. The risk of osteonecrosis of jaw and atypical fracture have been shown to be associated with prolonged use of BP. Hence it has been recommended to administer BP for 5 years in osteoporotic patients [32].

FDA and MHRA do not recommend the use of BP in patients with e GFR <30ml/min. Since BP have renal excretion, it may affect kidney function. Moreover, low BMD in CKD-MBD can be

either due to renal osteodystrophy or osteoporosis, and therefore suggesting a cautious use of BP in this subpopulation of CKD.

Administration of BP in CKD-MBD patients with low bone turnover can have adverse consequences in the form of over-suppression leading to ABD. This will further increase the risk of fractures and extra-skeletal calcification increasing the morbidity in this group of patient.

2.2.1. Nephrotoxic effect of BP

There is a concern regarding nephrotoxic effect of BP. There is substantial evidence, which state that BP increases serum creatinine and this has been seen in cancer patients receiving intravenous bisphosphonate therapy.

BP administered intravenously does have nephrotoxic effect and intravenous zoledronic acid increases serum creatinine levels. Ibandronic acid may be less problematic in this respect. Approximately 50% of oral bisphosphonate is renally eliminated and the pharmacokinetics in renal impairment has not been fully elucidated.

Despite several reports, nephrotoxicity is uncommon and rarely of clinical significance when lower (osteoporotic range) doses of BP are used. Renal toxicity with BP appears to be associated with both dose and infusion time. Some experts recommend lower dose of BP to prevent nephrotoxicity. However there is lack of evidence related to effect of BP on fracture risk and BMD in CKD-MBD. Very few studies have assessed the effect of BP on renal function and have shown no difference in serum creatinine in patients administered BP over a period of three years in CKD 2-4 [33]. Nevertheless, manufacturers do not recommend administration of BP in patients with e GFR less than 35ml/min in view of safety issues.

2.2.2. Effect of BP on bone turnover in CKD

The second area of concern relates to the skeleton itself. BP binds to hydroxyapatite and powerfully impairs resorptive activity, and thus reducing bone turnover rate. Since there are very few clinical trials involving small which have assessed the effect of BP on fracture risk in CKD-MBD, there is no clear evidence regarding its efficacy in this group of CKD. Therefore it is reasonable to administer BP only in those patients who have high bone turnover in CKD-MBD. However, BP need to be given cautiously in this group as they can reduce serum calcium levels by inhibiting bone resorption, thereby leading to secondary hyperparathyroidism which can be detrimental to bone. Additionally BP has a long retention time in bone, which can further induce parathyroid hyperplasia and can lead to adynamic bone. The incidence of ABD has increased in CKD patients particularly those on dialysis and BP administration can have deleterious effect. The risk of extra-skeletal calcification is high in ABD as it is associated with impaired ability of bone to buffer calcium. Moreover there is a increased risk of fracture in ABD which gets further aggravated by BP impairing the bone strength and quality.

Therefore patients with reduced bone turnover in CKD-MBD may benefit with anabolic therapy which will increase the bone formation. This will be a more logical approach in managing the bone metabolic disorder in CKD-MBD.

Hence the theoretical hypothesis does not favour the administration of BP in low bone turnover CKD-MBD. This implies that ideally bone biopsy should be performed before administration of BP in late CKD patients. However similar benefit might be obtained more simply by using indirect measures of biochemical markers of bone turnover such as BALP and PTH.

2.2.3. *Extra-skeletal calcification*

Vascular calcifications are a serious problem in patients with CKD-MBD. There has been suggestion that BP by reducing the bone turnover in CKD-MBD can exacerbate the risk of vascular calcification. The interaction between BP and vascular calcification is complex which is related to low bone turnover effect of BP. Several studies have shown that low bone turnover is unable to buffer calcium and phosphate load increasing the risk of vascular calcification [34]

2.2.4. *Effect of BP on fracture risk*

The patients with early CKD with no biochemical abnormalities will benefit from BP as shown in general population in terms of fracture prevention and risk [35,36].

The decision regarding BP use is more difficult in late CKD who present with bone mineral disorder and have been having fractures. Studies so far carried in late CKD are confined to stage 4, are post hoc analysis and have small sample size and thus difficult to interpret their results with regards to fracture risk in this sub-population [37]. There are no published data for the safety and efficacy of BP in patients with CKD 5/5D.

Recommendations

- BP is recommended for the treatment of osteoporosis in early CKD
- BP use in late CKD can be detrimental than beneficial due to concerns, around its appropriateness and safety
- There is no reliable evidence regarding the efficacy of BP in late CKD
- Since BP have longer bone retention, it may exacerbate the risk of vascular calcification and atypical fractures in late CKD patients

Role of Denosumab (DN)

Denosumab, a receptor activator of nuclear factor kappa-B ligand (RANKL) inhibitor, is not cleared by the kidney and may be safe in patients with CKD. DN inhibits the bone resorption by reducing the production of osteoclasts, thereby increasing the BMD at both lumbar and hip and reducing the vertebral and hip fractures [38].

DN unlike BP is not metabolized or excreted by the kidney and does not affect kidney function [39]. DN is recommended by FDA in patients with low eGFR. Since DN is metabolized by reticuloendothelial cells, it has a shorter duration of action lasting 3-6 months and therefore shorter retention time in bone. Efficacy and safety of DN in reducing fracture risk has been demonstrated in post hoc studies in CKD stage 4 [40]. Besides this it has a shorter retention time in bone [41]. Study by Jamal et al showed that DN significantly increased BMD and reduced fracture risk in postmenopausal women with CKD 1-4 [40].

Nonetheless, severe hypocalcaemia has been reported post DN in patients with late CKD or on dialysis [42]. It has been suggested that post DN therapy in CKD-MBD simulates the hungry bone syndrome. CKD-MBD is characterized by secondary hyperparathyroidism resulting in increased bone resorption. By giving DN in such patients there is inhibition of bone resorption, which promotes the bone uptake of calcium thereby causing severe hypocalcaemia. Thus patients with severe hyperparathyroidism with concomitant vitamin D deficiency are at potential risk of severe hypocalcaemia following DN [42]. Recent MHRA alert Oct 2012, has reported the risk of hypocalcaemia in patients with e GFR < 30 ml/min. Therefore MHRA recommends the supplementation of calcium and vitamin D in such patients to avoid hypocalcaemia.

DN is considered to be safe in late CKD as it does not affect renal functions and has shorter bone retention time. There is no evidence that DN over suppresses the bone turnover and potentiates the risk of ABD in late CKD. However, it has been suggested to carry out bone biopsy before administration of DN in CKD 5/5D.

Recommendation

- DN is recommended for the management of osteoporosis in early CKD
- DN is safe to administer in late CKD as it neither affects kidney function nor metabolized by kidney
- It has a shorter duration of action and has shorter retention time in bone, therefore its effect on bone turnover will reverse after an interval of 6 months
- Post hoc studies have shown that it increases BMD and reduces the fracture risk in CKD 4, nevertheless there is no evidence regarding its efficacy on bone in CKD 5/5D

Strontium Ranelate in CKD

The mode of action of SR is thought to be dual with both anti-resorptive and mild anabolic. It is approved for the treatment of postmenopausal osteoporosis as it reduces the risk of vertebral and hip fractures. Nevertheless, it is not recommended for the treatment of osteoporosis in patients with late CKD. Its use in early CKD for the management of osteoporosis is contraindicated in patients with cardiovascular diseases, uncontrolled hypertension and deep venous thrombosis.

Raloxifene

Raloxifene is a selective estrogen receptor modulator and is approved for the management of osteoporosis in postmenopausal women. It reduces the risk of vertebral fractures but has not been shown to reduce the hip fractures. Its use is contraindicated in patients with late CKD.

Teriparatide

Teriparatide is a human recombinant hormone that contains amino acid residues 1-34 of the 84 amino acid sequence of human PTH. It is an anabolic agent that has been shown to improve the spine and hip BMD and reduces the vertebral and non-vertebral fracture [43]. It is approved for the treatment of postmenopausal osteoporosis in women and in men. It has been recom-

mended to treat patients with severe osteoporosis with teriparatide who have been having recurrent fractures in spite of being on anti-resorptive treatment.

The safety and efficacy of teriparatide have been demonstrated in patients with early CKD (eGFR >30 mL/min), but there are no data on the use of this agent in patients with eGFR <30 mL/min. Teriparatide is contraindicated in patients with early CKD who have hypercalcaemia, elevated PTH, bone metabolic disorders other than osteoporosis and malignancy.

Calcium and vitamin D

In CKD patients with osteoporosis, calcium and vitamin D supplementation is recommended at the same dose as it is used for individuals with postmenopausal osteoporosis. Optimal calcium intake of 1200mg daily and optimal 25 (OH) D levels ≥ 75 nmol/L are suggested by various guidelines. Vitamin D supplementation in the form of cholecalciferol or vitamin D analogues is approved for the treatment of postmenopausal osteoporosis. It has been shown to reduce the risk of vertebral fractures in postmenopausal women with osteoporosis.

2.2.5. Recommendations on the treatment of osteoporosis in CKD

- BP is the first line of osteoporosis treatment in early CKD whereas it is not recommended for the treatment of low BMD in late CKD
- DN is safe to administer in late CKD
- DN should be given cautiously in late CKD as there is risk of hypocalcaemia and adynamic bone with its administration
- Adequate intake of calcium and vitamin D is important in patients with late CKD before DN therapy
- Before administration of DN, serum calcium should be within the reference range and 25 (OH) D levels should be ≥ 75 nmol/L in late CKD

3. Critical appraisal of evidence

3.1. Kidney Disease – Improving Global Outcomes (KDIGO) published the recommendations for the management of osteoporosis and CKD-MBD in CKD patients

KDIGO Clinical Practice Guidelines for the diagnosis, evaluation, prevention and treatment of Chronic Kidney Disease – Mineral and Bone Disorder (CKD-MBD) (Kidney Int. 2009; vol 76 suppl 113, s1-132]

Following are the recommendations made by KDIGO 2009 guideline in managing CKD-MBD

- The bone biopsy and histological/histomorphometric diagnosis is helpful in classification of CKD-MBD
- It is reasonable to perform a bone biopsy in various settings including: unexplained fractures, persistent bone pain, unexplained hypercalcaemia, unexplained hypophospha-

temia, possible aluminum toxicity, and prior to anti-resorptive therapy in patients with osteoporosis

- BMD does not predict fracture in CKD-MBD and should not be used routinely
- Serum 25 (OH) D should be measured routinely and corrected
- Monitor serum levels of calcium, phosphorus, PTH, and alkaline phosphatase activity
- Measurements of serum PTH or BALP can be used to evaluate bone disease because markedly high or low values predict underlying bone turnover
- Routine measurement of bone-derived turnover markers of collagen synthesis such as P1CP/P1NP and breakdown such as CTX, NTX, PDY, DPYD is not recommended
- Patients with levels of intact PTH above the upper normal limit of the assay need to be evaluated for hyperphosphatemia, hypocalcaemia, and vitamin D deficiency
- It is reasonable to correct these abnormalities with any or all of the following: reducing dietary phosphate intake and administering phosphate binders, calcium supplements, vitamin D supplements and calcimimetics
- In patients with persistently high serum PTH, treatment with calcitriol or vitamin D analogs is suggested
- In patients with CKD stage 5D, maintaining PTH levels in the range of approximately two to nine times the upper normal limit for the assay

3.2. Suggested protocol for management of osteoporosis in CKD

CKD 1-3 (early CKD)

- DEXA: T scores suggest osteoporosis
- Treat as postmenopausal osteoporosis

CKD 4-5 /dialysis (e GFR ≤ 30 or late CKD)

- DEXA not helpful in predicting osteoporosis and does not predict fracture risk
- Bone fragility fracture can be due to renal osteodystrophy/ osteoporosis
- Biochemical markers: BALP and PTH may be used to assess the bone turnover

Increased bone turnover

Raised BALP and PTH

- Exclude other causes of raised bone markers before treating high bone turnover:
 - Vitamin D deficiency
 - Hypocalcaemia
 - Hyperphosphatemia

If any of THE above present than correct and recheck BALP and PTH

- If vitamin D sufficiency ($\geq 75\text{nmol/L}$) WITH serum adjusted calcium and serum phosphate levels within the reference range
 - Administer Denosumab 60mg subcutaneous
 - Monitor BALP after therapy every 6 months
 - Administer further Denosumab only if there is a rise in BALP

Reduced bone turnover

Normal BALP and normal PTH/mildly elevated PTH

- No treatment with anti-resorptive therapy

4. Summary

Osteoporosis in early CKD is treated similar to general population. In late CKD or CKD-MBD, it is difficult to identify the type of bone metabolic disorder. Moreover, treatment of bone metabolic disorders is complicated by mineral and hormonal disturbances seen in late CKD. Also, there is a high prevalence of ABD in CKD-MBD and administration of anti-resorptive potentiates the risk of ABD or vascular calcification. Hence judicious use of anti-resorptive therapy is required in late CKD.

Following protocol can be followed for the management of Osteoporosis in late CKD or CKD-MBD:

- There are no published data on the safety and efficacy of any approved agent for osteoporosis among men and women with eGFR <30 or in late CKD
- In clinical practice, at the current time and with current limited knowledge, treatment of osteoporosis in stage 4-5/D CKD or late CKD is opinion based
- A reasonable clinical approach would be to consider therapy only in those with bone fragility fractures
- After exclusion of ABD (low bone turnover) and osteomalacia (vitamin D deficiency); high bone turnover should be considered for treatment with anti-resorptive therapy
- Osteoporosis in CKD-MBD is a diagnosis of exclusion
- Correct the biochemical abnormalities associated with CKD-MBD i.e. calcium and phosphate within the reference range; optimal vitamin D levels ($\geq 75\text{nmol/L}$)
- Increased bone turnover is indicated by: raised BALP after correction of calcium, phosphate and vitamin D levels (as mentioned above)
- Avoid DEXA: poor association of BMD with fracture risk

- Low BMD is not an indicator of treatment with anti-resorptive therapy
- Denosumab is the preferred treatment and should be administered after correcting calcium and vitamin D status
- Avoid Denosumab in severe hyperparathyroidism (>30pmol/L) as there is a risk of hypocalcaemia
- Post Denosumab therapy: check BALP every 6 monthly to assess the response to treatment
- Administer Denosumab only if there is rise in BALP

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The aim of this article will be to critically analyse the evidence available with regards to management of osteoporosis in chronic kidney diseases (CKD)

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