



Chronic kidney disease mineral bone disorder

DRAŠKO PAVLOVIĆ¹
DAJANA KATIČIĆ¹
TONKO GULIN¹
JOSIPA JOSIPOVIĆ¹
LIDIJA ORLIĆ²

¹ Department of Nephrology and Dialysis
Sestre Milosrdnice University Hospital, Zagreb,
Croatia

² Department of Nephrology
Dialysis and Kidney Transplantation
University Hospital Centre, Rijeka, Croatia

Correspondence:

Doc. dr. sc. Draško Pavlović
Sestre Milosrdnice University Hospital,
Vinogradska c.29
10000 Zagreb
E mail: drasko.pavlovic@kbcsm.hr

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Abstract

Chronic kidney disease – mineral bone disease (CKD-MBD) is a syndrome defined as a systemic mineral metabolic disorder associated with CKD. The term renal osteodystrophy, as a part of CKD-MBD, indicates a pathomorphological concept of bone lesions. High morbidity and mortality of CKD patients is a consequence of CKD-MBD. The pathogenesis of this syndrome is not completely understood, but undoubtedly the development of mineral and bone disorder begins in the earliest stages of CKD. The diagnosis is made by non-invasive methods (biochemistry, x-ray, ultrasound, etc.) and bone biopsy as an invasive method. In addition to new drugs, e.g. non-calcium phosphate binders, vitamin D analogs, calcimimetics, prevention and treatment is still a major challenge for the nephrologist. In this article we will briefly discuss the pathophysiology, diagnosis, prevention and treatment of CKD-MBD.

Chronic kidney disease (CKD), defined by structural or functional kidney abnormalities for more than three months, is a significant global health problem. Based on kidney function, i.e. glomerular filtration rate (GFR), CKD is classified in five stages: stage 1: GFR > 90 ml/min, stage 2: GFR 60-89 ml/min, stage 3: GFR 30-59 ml/min, stage 4: GFR 15-29 ml/min and stage 5: GFR ≤15 ml/min. CKD is associated with multiple organ dysfunctions. Due to the high prevalence of cardiovascular disease, the mortality of CKD patients is very high. In addition to traditional risk factors for cardiovascular disease (hypertension, diabetes, hyperlipidemia), there are many other non-traditional risk factors. Mineral disturbance is one of the most important non-traditional risk factors (1).

The kidney has a central role in the maintenance of serum calcium and phosphorus levels through tubular reabsorption mechanisms. Parathyroid hormone (PTH), vitamin D, i.e. calcitriol and fibroblast growth factor 23 (FGF 23) are important factors in the regulation of calcium and phosphorus metabolism. These factors are also involved in bone metabolism and are interrelated, i.e. they are the basis for the bone-kidney axis. In patients with impaired kidney function, even in the early stages of impaired metabolism of calcium, phosphorus and regulatory hormones occur. The consequence is bone disease (2).

Bone disease, known as renal osteodystrophy, was recognized as a complication of chronic renal failure (today CKD stage 5) in the early of 1960s (3). Since then, great advances have been made in diagnosis, prevention and treatment. At the same time, it has been recognized that

TABLE 1

KDIGO definition of CKD MBD and renal osteodystrophy (ROD) , (adapted from ref. 5).

<p>CKD MBD, a systemic disorder of bone and mineral metabolism due to CKD, manifested by following:</p> <ul style="list-style-type: none"> • Abnormalities of calcium, phosphorus, PTH, vitamin D • Abnormalities in bone turnover, mineralization and volume • Vascular or other soft tissue calcification <p>ROD, a bone disease in CKD with the following characteristics:</p> <ul style="list-style-type: none"> • Alteration of bone morphology • One measure of the skeletal component of CKD MBD quantifiable by histomorphometry of bone biopsy
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bone disease is only one of a broad spectrum of imbalances that manifests itself in pathological changes in the bones and very often in pathological changes outside of the skeleton, particularly heart and vessels (4). In 2006, a new definition came into use: chronic kidney disease-mineral and bone disorder (5). It describes a very broad clinical syndrome, i.e. a systemic disorder of mineral and bone metabolism due to CKD, manifested by abnormalities of calcium, phosphorus, PTH, vitamin D, FGF 23, bone diseases and significant pathologic calcification (Table 1).

THE PATHOGENESIS OF CKD-MBD

The pathogenesis of CKD-MBD is not completely understood, but based on broad basic and clinical research it is accepted that a central role in pathogenesis is phosphorus (better to say phosphate, since we measure phosphate in a blood sample) retention (Table 2) (6). Due to impaired kidney function, there is reduced phosphate excretion that leads to phosphate retention. As a result of that phosphate retention, there is increased secretion of FGF 23 on one hand and impaired synthesis of calcitriol on the other. Reduced synthesis of calcitriol is the result of reduced renal mass, phosphate retention and the effect of increased FGF 23 level. A low level of calcitriol together with phosphate retention leads to hypocalcaemia. The net effect is increased synthesis and secretion of PTH (Figure 1). In the early stages of CKD hyperphosphatemia and hypocalcaemia are counteracted by increased PTH concentrations. Therefore, in many patients normal levels of calcium and phosphate are present, but the price is a high PTH level. As with other endocrine organs, parathyroid gland (PTG) overactivity is associated with hypertrophy and hyperplasia. The characteristic of PTG hyperplasia in CKD patients is initially diffuse and polyclonal, after which nodular change appear, i.e. monoclonal hyperplasia, with a significant reduction of vitamin D and calcium receptors (7, 8). The result is secondary hyperparathyroidism. In this brief description of the pathogenesis of secondary hyperparathyroidism it must be emphasized that, based on very recent research, FGF23 and its co-receptor klotho (transmembrane receptor) probably have the most important roles. A reduced number of klotho receptors in kidney and parathyroid glands

and an increased level of FGF23 leads to hypocalcemia, hyperphosphatemia, reduced level of calcitriol and PTH overactivity (2, 6).

Increased bone turnover with a tendency to fracture is the result of hyperparathyroidism (6, 9).

The other extreme of bone disease in CKD is low bone turnover, i.e. adynamic bone disease. Until the early 1980s, aluminum intoxication was the main cause of low bone turnover disease in CKD patients. Today, the risk factors for this form of bone disease in CKD patients are patient age, diabetes mellitus, inadequate treatment with active vitamin D analogs or calcium- based phosphate binders (i.e. excess calcium load), etc. (2, 9). Bone pain and the risk of fractures are also manifestations of this form of renal osteodystrophy.

Finally, soft tissue calcification and vascular calcifications are the results of increased phosphate levels. There is much data to confirm the possibility of transforming the smooth muscle cells in the arterial wall into an osteoblast-like cell. Vascular calcification, as part of CKD-MBD syndrome, is different from that seen in the general population. In the aging general population calcification of intima occurs, while in CKD patients calcification of arterial media is more prominent. The result is greater vascular stiffness, hypertension, and left ventricular hypertrophy (10, 11).

CLINICAL MANIFESTATION OF CKD-MBD

Bone and mineral disturbance in CKD patients can be asymptomatic for a long time. The first manifestation of CKD-MBD is biochemical. Bone and muscle pain, weakness and fractures of bone and sometimes avascular necrosis can be seen in later stages of the disease. The incidence of bone fractures is very high in CKD patients. It is twice as high compared to patients without CKD. In severe forms of CKD-MBD osteoclastomas, or brown tumors resulting from PTH- stimulated osteoclastic activity can be seen (12). Calcific uremic arteriolopathy, a condition in which small cutaneous blood vessels are calcified, is often lethal and is seen in severe secondary hyperparathyroidism (3, 9).

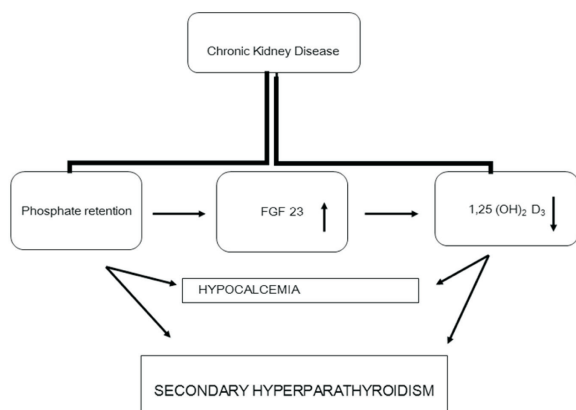


Figure 1. Pathogenesis of secondary hyperparathyroidism. (FGF 23 fibroblast growth factor 23).

DIAGNOSIS OF CKD-MBD

CKD-MBD is asymptomatic for a long time. Therefore, diagnosis is based on biochemistry, radiology and finally on a bone biopsy. The key measurements used in routine CKD-MBD screening are calcium, phosphate, alkaline phosphatase and PTH. Based on the Kidney Disease Outcomes Quality Initiative (KDOQI) and the Kidney Disease Improving Global Outcomes (KDIGO) guidelines, these measurements should be routinely monitored beginning at stage 3 CKD. (1, 5, 13) Prevention and treatment should be guided by these measurements. A physician involved in the treatment of CKD patients should interpret them carefully. Total calcium, but not ionized calcium, should be checked regularly. The so-called corrected calcium can be calculated by adding 0.2 mmol to the total calcium for every 1 g/L decrease in the albumin level below 40 g/L. The calcium concentration cannot be a guide for the underlying CKD-MBD (1). There is diurnal and postprandial variation of the phosphate level. Therefore, the phosphate level should be checked on an empty stomach. Total alkaline phosphatase is not the best marker for bone turnover, but an immunoassay for bone specific alkaline phosphatase as better marker is not in standard practice.

There is no doubt that measurement of PTH is most important in the diagnosis of CKD-MBD. Once again, the results should be interpreted carefully. The routine assay for PTH is so-called intact PTH. With this assay, also called the second generation, some fragments (C-terminal) antagonistic to intact PTH are detected. Therefore the optimal level of PTH is not known, but it should be more than three times the upper limit of normal. It is more important to check the PTH level a few times per year in CKD patients (there are some suggestions that it should be done monthly) and to follow the trend of the PTH level (1, 13).



Figure 2. Subperiosteal resorption of the bone of the middle phalanx (arrows).

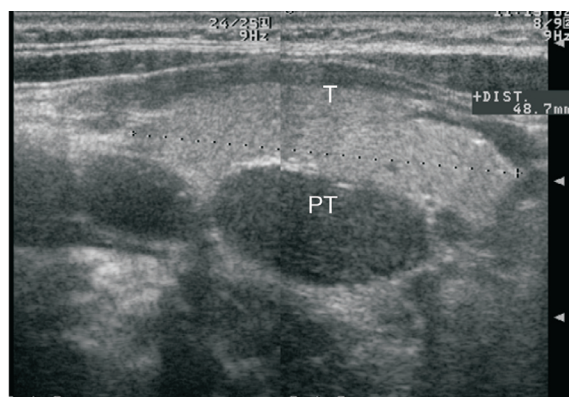


Figure 3. Parathyroid sonography (PT parathyroid gland, T thyroid gland).

Imaging by X-ray, ultrasound, computed tomography and magnetic resonance of the skeleton is relatively insensitive for a diagnosis of CKD-MBD. (3, 9) The results of bone densitometry should also be interpreted carefully and it cannot distinguish between osteoporosis and CKD-MBD (14). The characteristic X-ray changes in CKD-MBD are the phalangeal tufts, subperiosteal bone erosion (Figure 2), lineal osteosclerosis of the spine, and lucent areas of the long bones (very often brown tumor). In our experience ultrasound is very useful in detecting PTG size and shape, i.e. to make a diagnosis of PTG hyperplasia and to distinguish diffuse and nodular hyperplasia. Nodular hyperplasia is a more severe form of hyperplasia (Figure 3) (7, 8).

TABLE 2

PTH, calcium and phosphorus target values according to KDOQI and KDIGO guidelines.

CKD stage	Calcium mmol/l		Phosphorus mmol/l		PTH pg/ml	
	KDOQI	KDIGO	KDOQI	KDIGO	KDOQI	KDIGO
3	Normal range	Normal range	0,86-1,47	Normal range	35-70	Normal range
4	Normal range	Normal range	0,86-1,47	Normal range	70-110	Normal range
5	2,1-2,4	Normal range	1,12-1,76	Toward the normal range	150-300	2-9 time the upper normal limit

Bone biopsy is the gold standard for a diagnosis of the pattern of bone disease, but it is not available everywhere, and it is invasive and time consuming. In more recent guidelines there is new classification system for bone histomorphometry, known as turnover mineralization and volume (TMV). Instead of the terms of adynamic bone, mixed or mild osteodystrophy, and high turnover bone disease (osteitis fibrosa), the TMV classification is made up of different descriptors: T (from low to high), M (from normal to abnormal), and V (from low to high). The bone biopsy should be done if a prediction by non-invasive methods of bone changes is very weak (1, 15).

PREVENTION AND TREATMENT OF CKD-MBD

The central tenets of treatment of CKD-MBD are correction of hypocalcaemia, reducing hyperphosphatemia, and maintaining optimal concentration of calcitriol. Unfortunately, it is still difficult to control mineral disturbance, including increased PTH synthesis and secretion. In the last ten years, several guidelines for the diagnosis and treatment of CKD-MBD have been published (1, 5, 13). There are many differences between guidelines, and the majority of statements in these guidelines are based on evidence graded as poor or moderate (16, 17, 18). However, treatment paradigms today have centered on the adoption of KDOQI or KDIGO guidelines (Table 2).

PHOSPHORUS CONTROL

Dietary phosphorus restriction to less than 1000 mg/day is recommended. Food with high phosphorus content (high phosphorus to protein ratio) and food and drinks with a high level of phosphate additives, such as some soft drinks, e.g. coca cola, and fast and processed foods should be avoided. Dietary restriction is insufficient in the majority of patients, particularly those on dialysis. They must use phosphate binders. Calcium-based binders are effective, but hypercalcemia can be a possible side effect. A combination of calcium acetate and magnesium carbonate has several advantages. Magnesium can reduce the risk of soft tissue calcification. Sevelamer carbonate, a

non-calcium-based phosphate binder is effective, with the possibility of decreasing low-density lipoprotein cholesterol levels. Lanthanum carbonate is also an effective phosphate binder, but it is still unavailable in many countries. Phosphate binders should be taken at each meal. High pill burden is a major reason for poor adherence by CKD patients. Dialysis adequacy is important in reducing phosphate level, and even more important is more frequent dialysis, e.g. short daily or long nocturnal hemodialysis (19).

Vitamin D Therapy

Vitamin D or analogs are often used in CKD patients to prevent and treat secondary hyperparathyroidism. For many years, the most commonly used agent was calcitriol (in some European countries it was alfacalcidol). Today, paricalcitol, a less calcemic vitamin D analog also called selective vitamin D receptor activator, is used more frequently (6).

Calcimimetics

A calcimimetic, cinacalcet, is an allosteric activator of calcium-sensing receptors. Cinacalcet offers a new therapeutic modality by reducing parathormone synthesis secretion and hypercalcemia. On the other hand, hypocalcaemia could be a negative side effect. Vitamin D analogs and calcimimetics can be used together (6, 13).

Surgery

In some patients, even with new drugs, severe hyperparathyroidism could be present and surgery becomes inevitable. Total parathyroidectomy, with or without autotransplantation, or a subtotal parathyroidectomy, could be performed. If surgery is indicated, very often in patients with severe nodular PTG hyperplasia, it should be done before a kidney transplant (8, 20).

CONCLUSION

CKD-MBD could be a significant cause of morbidity and mortality in CKD patients. The prevention and

treatment of CKD-MBD is still a major challenge for the nephrologist (8). New international and many national guidelines might be helpful, but one should remember that guidelines should inform but not dictate, guide but not enforce, and support but not restrict (21).

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