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Pathogenesis and Treatment of Chronic Kidney Disease-Mineral and Bone Disorder

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1. Introduction

The prevalence of chronic kidney disease (CKD) is increasing, and CKD patients are at risk for severe adverse outcomes such as progressive loss of kidney function, cardiovascular (CV) disease, and premature death [1]. CKD-Mineral and Bone Disorder (CKD-MBD) is the clinical syndrome that develops as a systemic disorder of bone and mineral metabolism due to CKD, which is manifested by abnormalities in bone and mineral metabolism [1]. Alterations in calcium and phosphate metabolism that are frequently observed in secondary hyperparathyroidism of uremia (SHPT), particularly in patients with maintenance hemodialysis, contribute to ectopic calcification, CV disease, and the risk of death [2].

SHPT is associated with various bone diseases including osteitis fibrosa caused by excessive secretion of parathyroid hormone (PTH), osteomalacia, adynamic bone disease, and combinations thereof; these diseases are collectively called renal osteodystrophy (ROD). In addition, ectopic calcifications such as soft-tissue and vascular calcifications are observed in patients with long-standing CKD. These patients are characterized by calcification of the vascular media, which is called Mönckeberg medial calcific sclerosis, and vascular intima, which is typically triggered by abnormal calcium and phosphorous metabolism due to SHPT [3]. Calcification of the vascular media is a particularly important factor for predicting CV mortality in dialysis patients. Elevation of the serum calcium \times phosphate product also increases the relative mortality risk. The abovementioned facts suggest that the pathology of CKD-MBD should be fully elucidated to prepare an appropriate treatment plan.

2. Calcium and phosphate homeostasis

Small changes in extracellular fluid calcium concentration have major effects on muscle contraction and neuronal excitability, as well as numerous cellular functions such as cell division, cell adhesion, plasma membrane integrity, and coagulation. However, the changes in serum phosphate concentration are asymptomatic in normally functioning kidneys. Severe chronic depletion may cause anorexia, muscle weakness, and osteomalacia. Hyperphosphatemia is also asymptomatic, although symptoms of hypocalcemia, including tetany, can occur when concomitant hypocalcemia is present.

Parathyroid hormone (PTH), the active form of vitamin D (1,25-dihydroxyvitamin D; 1,25-(OH)₂D), and fibroblast growth factor (FGF)-23, are the principal physiologic regulators of calcium and phosphate homeostasis in humans [4,5] (Figure 1). Feedback loops exist between ionized calcium (Ca²⁺), phosphate, 1,25-(OH)₂D, FGF-23, and PTH.

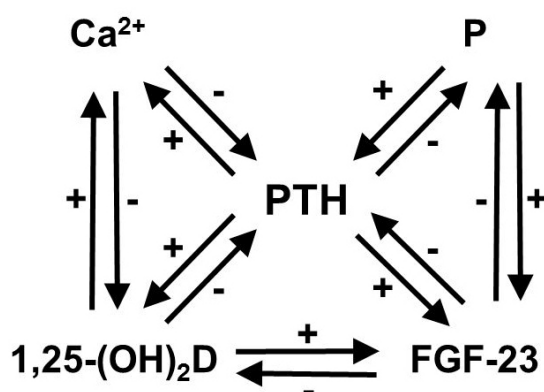


Figure 1. Feedback loops in calcium ion (Ca²⁺) and phosphate (P) homeostasis [4,5], modified from a previous report [8]. Feedback loops exist between Ca²⁺, P, 1,25-dihydroxyvitamin D (1,25-(OH)₂D), fibroblast growth factor 23 (FGF-23), and parathyroid hormone (PTH). Ca²⁺, 1,25-(OH)₂D, and FGF-23 suppress PTH secretion, whereas P overload accelerates it. P overload does not always cause the elevation of serum phosphate, with the exception of some conditions such as chronic kidney disease.

2.1. Parathyroid Hormone (PTH)

The extracellular fluid Ca²⁺ concentration is the primary regulator of the rapid (in minutes) synthesis and secretion of PTH. An inverse relationship was observed between the extracellular fluid Ca²⁺ concentration and PTH secretion from parathyroid cells *in vitro* [6] (Figure 2). Hypersecretion of PTH causes hypophosphatemia due to hyperphosphaturia in normally functioning kidneys; however, it leads to hyperphosphatemia by mobilization of phosphate from skeletal tissues in CKD, particularly in hemodialysis patients.

2.2. 1,25-dihydroxyvitamin D (1,25-(OH)₂D)

In contrast to the rapid action of PTH, 1,25-(OH)₂D contributes to long-term calcium homeostasis. 1,25-(OH)₂D also elevates serum phosphate concentration by promoting incremental intestinal phosphate absorption.

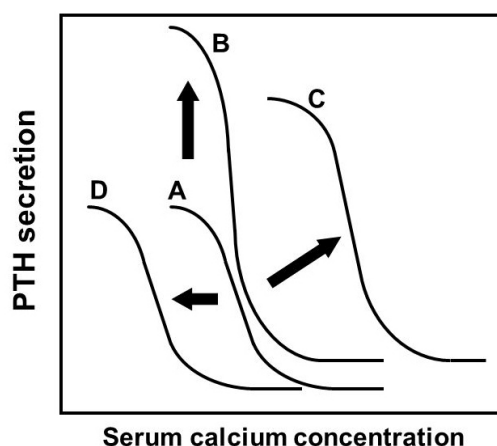


Figure 2. Pathogenesis of secondary hyperparathyroidism of uremia (SHPT) [56], modified from a previous report [26]. The analyses of PTH secretions inhibited by extracellular calcium *in vitro* revealed the sigmoidal relationship of the PTH–calcium relationship. Setpoint, the calcium concentration causing half-maximal inhibition of PTH secretion, is an indicator of sensitivity of parathyroid cells to extracellular calcium by CaR. (A) The relationship in healthy subjects was fitted to a symmetrical sigmoidal curve. (B) The normal sigmoidal curve will shift upward when the secretory cell number is increased, without changing its setpoint. (C) An altered sigmoidal curve is observed in human parathyroid adenomas, refractory SHPT, by changing the setpoint to the right. In the case of severe setpoint shift, PTH secretion is persistent even at high calcium concentration: so-called ‘autonomous’ PTH secretion. An altered PTH–calcium relationship was also observed in PTH-cyclin D1 transgenic mice [4, 52]. (D) Administration of cinacalcet or activating mutation of CaR observed in autosomal dominant hypocalcemia increases the CaR sensitivity to serum calcium. Activations of CaR result in the PTH–calcium relationship curve moving to the left.

2.3. Fibroblast Growth Factor 23 (FGF-23)

FGF-23, a member of the FGF family, is a major phosphaturic factor in the development of hypophosphatemic rickets/osteomalacia, including X-linked hypophosphatemic rickets (XLH) and oncogenic osteomalacia [7]. FGF-23 suppresses both PTH secretion and its expression in parathyroid cells [8]. PTH also stimulated FGF-23 expression and its secretion in bone [9], suggesting that a negative feedback loop exists between PTH and FGF-23 [4,5] (Figure 1).

3. Receptors in parathyroid cells

The 3 parathyroid cell receptors that are important in calcium and phosphate homeostasis include the calcium-sensing receptor (CaR) and the FGF receptor (FGFR)-Klotho complex located on the cell surface and nuclear vitamin D receptor (VDR) (Table 1). CaR

and VDR are target molecules for the treatment of hyperfunctioning parathyroid diseases in CKD patients.

| Receptor | Location |
|----------------------------------|---------------|
| 1. Vitamin D receptor; VDR | cell nucleus |
| 2. Calcium-sensing receptor; CaR | cell membrane |
| 3. FGFR-Klotho complex | cell membrane |

Table 1. Receptors in parathyroid cells

3.1. Calcium-Sensing Receptor (CaR)

CaR contains a characteristic G protein-coupled receptor 7 membrane-spanning motif with an unusually large N-terminal extracellular domain, which was cloned in 1993 [10]. Positional cloning approaches have clarified that loss-of-function mutations in the *CaR* gene cause familial hypocalciuric hypercalcemia (heterozygous mutations) and neonatal severe hyperparathyroidism (homozygous mutations) [11].

Heterozygous *CaR* knockout mice exhibited a phenotype that was similar to that of familial hypocalciuric hypercalcemia [12]. Serum PTH levels were inappropriately elevated; however, the parathyroid glands were not enlarged in the heterozygous knockout mice. Homozygous knockout mice demonstrated markedly elevated serum calcium and PTH concentrations, retarded growth, and premature death [12]. These symptoms are similar to those of human neonatal severe hyperparathyroidism.

Synthetic allosteric modulators of CaR have been developed that act as either positive modulators (calcimimetics) or negative modulators (calcilytics). These ligands do not activate the wild-type receptor directly, but rather shift the PTH-calcium sigmoidal curves to the left or right, respectively (Figure 2).

3.2. Vitamin D Receptor (VDR)

1,25-(OH)₂D is the major steroid hormone that plays a crucial role in calcium and phosphate homeostasis, and its actions are mediated by VDR. Hereditary hypocalcemic vitamin D-resistant rickets (HVDDR) is an autosomal recessive disorder that is caused by inactivating mutations in the *VDR* gene, resulting in target tissue insensitivity to 1,25-(OH)₂D [13].

VDR knockout mice exhibit hypocalcemia, hypophosphatemia, rickets, alopecia, and hyperparathyroidism with enlarged parathyroid glands, similar to HVDDR [14,15]. Tissue-specific ablation of *VDR* in parathyroid tissue results in decreased parathyroid CaR expression and moderately increased basal PTH levels; however, no significant abnormalities in PTH-calcium sigmoidal curves were observed [16], suggesting limited roles of *VDR* in parathyroid pathophysiology.

3.3. FGF Receptor (FGFR)-Klotho complex

Klotho, which is expressed in kidney and pituitary and parathyroid glands, converts FGFR1, a canonical receptor for various FGFs, into an FGF-23-specific receptor [17]. FGF-23 null mice exhibit various senescence-like phenotypes such as a short lifespan, infertility, atrophy of the lymphopoietic and reproductive organs, decreased bone mineral density, and ectopic calcification. This phenotype is similar to that of Klotho-deficient mice [18], suggesting that FGF-23 signaling is Klotho dependent.

4. Chronic Kidney Disease – Mineral and Bone Disorder (CKD-MBD)

It is widely known that the progression of CKD increases mortality risk and the incidence of CV events [19]. Hyperphosphatemia is a critical electrolyte abnormality in patients with CKD-mineral and bone disorder (CKD-MBD) [20]. Even though hemodialysis or peritoneal dialysis is given to hyperphosphatemia patients with advanced CKD, these therapies are ineffective due to insufficient phosphorus-removal ability.

4.1. Calcium and phosphate metabolism in CKD-MBD

FGF-23 is involved in abnormal calcium and phosphate metabolism in CKD patients as the disease progresses. A cross-sectional study of 80 CKD patients revealed decreases in estimated GFR (eGFR), serum calcium, and 1,25-(OH)₂D levels as well as increases in serum P, fractional excretion of phosphate, PTH, and FGF-23 [21].

Further study of the abovementioned data revealed an increase in serum FGF-23 level (eGFR 45~60 mL/min), which is an independent predictor of the fractional excretion of phosphate, far earlier than the increase in serum phosphate levels (eGFR <30 mL/min). The increase in FGF-23 level is one of the greatest independent predictors of decreased 1,25-(OH)₂D level, independent of serum phosphate and eGFR. This suggests that the increase in FGF-23 level is the main reason for the decrease in 1,25-(OH)₂D level in CKD progression. Thus, the increase in FGF-23 level compensates for the increase in the serum phosphate levels caused by the decrease in nephrons associated with CKD progression by increasing the fractional excretion of phosphate. However, the increase in FGF-23 level also decreases the level of 1,25-(OH)₂D, which promotes PTH secretion and accelerates the progression of SHPT.

4.2. Vascular calcification in CKD-MBD

In an experiment using human vascular smooth muscle cells, inorganic phosphate transport into the cells via type III Na-Pi co-transporter (Pit-1) increased as the extracellular phosphate concentration increased. The increase in the intracellular phosphate concentration induced the expression of marker genes of apoptosis and osteogenic/chondrogenic cells in the vascular wall cells, which resulted in calcification [22]. This finding also implies a relationship between blood vessel calcification and phosphate levels *in vitro*.

Maintenance hemodialysis patients often develop blood vessel calcification, which is directly proportional to the duration of dialysis, irrespective of their age; this condition is characterized by calcification of the vascular media called Mönckeberg sclerosis rather than calcification of the vascular intima. The onset of blood vessel calcification in dialysis patients is mainly caused by abnormal calcium and phosphate metabolism due to SHPT [3], which is one of the signs of CKD-MBD. Calcification of the iliac artery [23] and abdominal aorta [24] are critical predictors of CV mortality in dialysis patients.

4.3. Renal Osteodystrophy (ROD)

ROD is a mineral and bone disorder that occurs as a complication of CKD, which exacerbates bone fragility and fracture [1]. The serum phosphorus concentration was significantly related to hospitalization for fracture [2]. Old age, dialysis vintage, female gender, white race, and lower body weight were significantly associated with an increased risk of fracture-related hospitalization.

In CKD patients, ROD manifests as alterations in bone morphology, such as osteitis fibrosa cystica, mild hyperparathyroid-related bone disease, osteomalacia, adynamic bone disease, and mixed uremic osteodystrophy. ROD represents histopathologic changes observed in bone and is typically characterized by changes in bone turnover, volume, and mineralization (TMV) (Table 2). The TMV classification, assessed by histomorphometry, provides a clinically relevant description of the underlying bone pathology and helps define the pathophysiology of the disease.

| Turnover | Mineralization | Volume |
|----------|----------------|--------|
| Low | Normal | Low |
| Normal | Abnormal | Normal |
| High | | High |

TMV: bone turnover, mineralization, and volume

Table 2. TMV classification for renal osteodystrophy (ROD) [1]

5. Pathogenesis of Secondary Hyperparathyroidism of uremia (SHPT)

PTH secretion increases when the glomerular filtration rate (GFR) of CKD patients decreases to 40–50 mL/min or less [25]. Renal impairment decreases urinary phosphate excretion, gradually leading to hyperphosphatemia. Phosphate accumulation in the body reduces 1α hydroxylase activity in the kidneys and suppresses vitamin D activation, which results in decreased serum active vitamin D ($1,25\text{-(OH)}_2\text{D}$) levels [26] (Figure 3). Hyperphosphatemia causes hypocalcemia by directly affecting the parathyroid glands; moreover, impaired vitamin D activation promotes PTH synthesis and secretion [27], which induces the proliferation

of parathyroid cells and parathyroid hyperplasia. This change stimulates excessive PTH activity and allows phosphates of the bone to move into the blood, exacerbating the hyperphosphatemia. Even though hemodialysis or peritoneal dialysis is given to hyperphosphatemia patients with advanced CKD, these therapies are ineffective due to the patients' insufficient phosphate-removal ability.

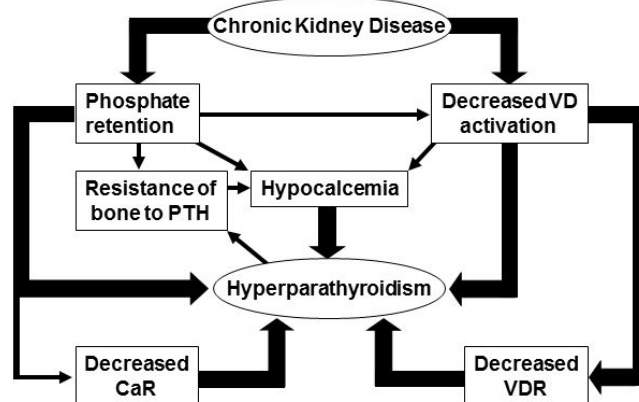


Figure 3. Pathogenesis of parathyroid tumorigenesis [4]. (A) A set of somatic mutations (hits) confers a growth advantage to an affected cell. Monoclonal growth renders the cells susceptible to more somatic mutations (hits), which leads to clonal evolution. (B) A uremic status such as chronic hypocalcemia, decreased levels of serum 1,25-(OH)₂D, and hyperphosphatemia stimulates parathyroid cell growth and leads to multi-glandular polyclonal hyperplasia. These hyperplastic parathyroid cells are susceptible to somatic mutations (hits), resulting in monoclonal growth.

In the earliest stages of CKD, the parathyroid glands undergo multi-glandular generalized hyperplasia, presumably a true polyclonal expansion, in response to stimuli that may include chronic hypocalcemia, decreased levels of serum 1,25-(OH)₂D, and hyperphosphatemia. However, in the late stage of this disease, usually after many years of dialysis treatment, a subset of patients develop refractory SHPT in which excessive PTH secretion no longer responds to physiological influences or standard medical therapy. Therefore, medically refractory SHPT is quite different from the readily managed SHPT, which is characterized by an abnormal PTH-calcium secretory relationship [28,29], is “autonomous,” and is typically treated by surgical parathyroidectomy. VDR [30] and CaR [31] expression was reduced in the parathyroid tumors of these patients.

The majority of surgically removed uremic parathyroid glands were confirmed to be monoclonal neoplasms by X-chromosome inactivation analysis [32]. This monoclonality implies that somatic mutation of certain genes controlling cell proliferation occurred in a single parathyroid cell, conferring a selective growth advantage upon it and its progeny (Figure 4). Distinct chromosomal abnormalities in sporadic parathyroid adenomas [33] and uremia-associated parathyroid tumors [34] revealed that the molecular pathogenesis of tumorigenesis in these 2 categories of parathyroid tumors was different. However, the major genes involved in the pathogenesis of SHPT remain unknown.

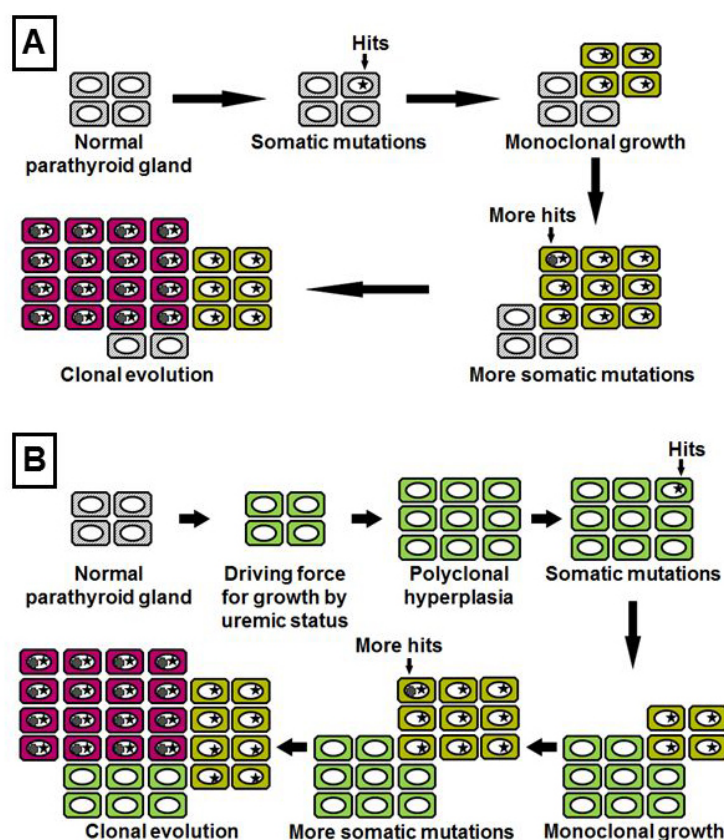


Figure 4. The sigmoidal curve of the PTH-calcium relationship [56]. The analyses of PTH secretions inhibited by extracellular calcium *in vitro* revealed a sigmoidal PTH-calcium relationship [6]. The setpoint, the calcium concentration causing half-maximal inhibition of PTH secretion, is an indicator of sensitivity of parathyroid cells to extracellular calcium by the calcium receptor (CaR). (A) This relationship in healthy subjects was fitted to a symmetrical sigmoidal curve. (B) The normal sigmoidal curve will shift upward when secretory cell number is increased without changing its setpoint. (C) An altered sigmoidal curve is observed in human parathyroid adenomas, refractory secondary hyperparathyroidism of uremia, with the setpoint shifting to the right. In the case of severe setpoint shift, PTH secretion is persistent even at high calcium concentrations, due to so-called “autonomous” PTH secretion. An altered PTH-calcium relationship was also observed in PHPT model mice [4,52]. (D) Administration of calcimimetics or the presence of an activating mutation of CaR in autosomal dominant hypocalcemia (ADH) patients [57] increased the sensitivity of CaR to serum calcium concentration in parathyroid cells. Activations of CaR result in a shift of the PTH-calcium relationship curve to the left.

Reduced expression of Klotho and FGFR1 was noted in the hyperplastic parathyroid glands of SHPT patients [35], suggesting that reduced FGF-23 signaling in parathyroid cells plays a role in the development of SHPT. However, some studies of Klotho expression in uremic animals reported conflicting results [36-38]. Further studies are necessary to clarify the role of FGFR-Klotho signaling in uremic parathyroid glands.

6. Guidelines for CKD-MBD

The National Kidney Foundation Kidney Disease Outcomes Quality Initiative (K/DOQI, USA) published the “K/DOQI clinical practice guidelines for bone metabolism and disease in chronic kidney disease” in 2003 as evidence-based clinical practice guidelines [39]. In

2005, according to “Definition and classification of chronic kidney disease: a position statement from Kidney Disease: Improving Global Outcomes (KDIGO),” the term CKD-MBD was proposed, stating that the importance of bone and mineral metabolism in CKD should be conceptualized in terms of prognosis [20]; this means that bone and mineral metabolism in CKD can be considered a systemic disease. In 2009, KDIGO proposed the current clinical practice guidelines [40], which have been adopted in clinical settings.

7. Treatment of CKD-MBD

The risk of all-cause mortality and CV events in patients with CKD-MBD on maintenance hemodialysis is well established. A greater mortality risk associated with phosphate, followed by calcium and PTH levels, was reported [41]. These 3 parameters are not only the best surrogate markers but also the best targets for CKD-MBD treatment.

7.1. Phosphate-binding agents

All-cause mortality increased regardless of whether serum phosphate levels were higher or lower than the reference value, exhibiting a U-shaped distribution [42]. However, maintenance dialysis patients in stable condition are likely to develop hyperphosphatemia, indicating that hyperphosphatemia treatment should be a primary target. Diet therapy is the first-line therapy that can sufficiently control serum phosphate levels. If it is insufficient, phosphate binders are administered orally. Calcium-containing phosphate binder (e.g., calcium carbonate) have been used for a long time. However, concomitant use of active vitamin D products can lead to the development of hypercalcemia and increase serum calcium \times phosphate product levels. Therefore, non-calcium-containing phosphate binder such as sevelamer hydrochloride and lanthanum carbonate are widely used.

Although hyperphosphatemia is a risk factor for mortality in dialysis patients, the effects of restricting phosphorus intake in these patients are unclear. When oral phosphorus intake is controlled, serum phosphate levels decrease, but poor nutritional status occurs as well. Thus, it is difficult to judge the true effect of the restriction of phosphorus intake, although studies using phosphate binders have been performed.

The Accelerated Mortality on Renal Replacement (ArMORR) study is a 1-year observational cohort study of 10,044 hemodialysis patients in 1,056 medical institutions in the US. According to this study, the 1-year survival rate of 3,555 patients prescribed phosphate binders before or within 90 days of initiating dialysis was higher than that of 5,055 patients who were not treated with these agents during the same period [43]. That study also compared survival in a subcohort of patients treated and not treated with phosphate binders matched by their baseline serum phosphate levels (i.e., a propensity score matched cohort study) and concluded that the survival rate was greater in the treated group, demonstrating the positive effect of these agents on the survival rate (Figure 5).

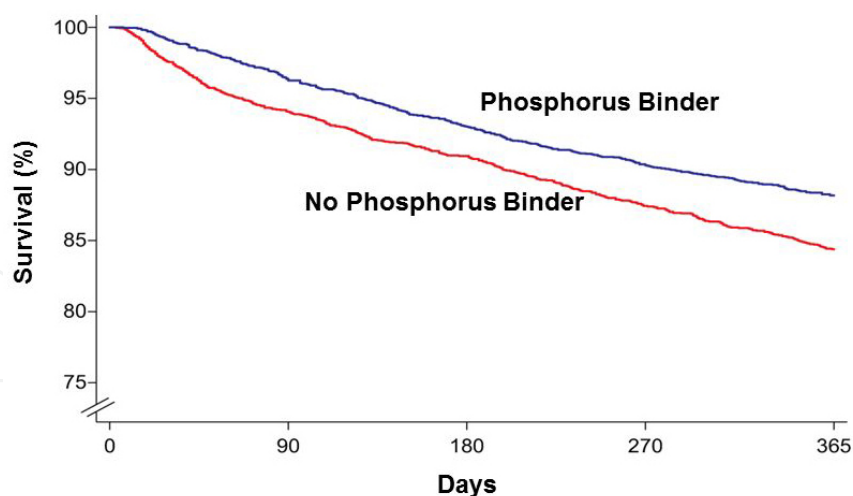


Figure 5. Survival of treated and untreated patients of the overall propensity score-matched cohort in the Accelerated Mortality on Renal Replacement (ArMORR) study [43]. A 1-year observational cohort study involving 10,044 dialysis patients in 1,056 medical institutions in the US studied the relationship between the effect of phosphate binders before and within 90 days of initiating dialysis and 1-year survival rate. The survival rate was greater in the group treated with phosphate binders. The subcohort study of patients treated and untreated with phosphate binders, matched by their baseline serum phosphate levels (i.e., the propensity score matched cohort), also demonstrated that the treated group had a better survival rate, demonstrating the positive effect of these agents on survival.

Many studies on maintenance dialysis patients have been performed. What about studies on patients who have just started dialysis? The Choices for Healthy Outcomes in Caring for End-Stage Renal Disease (CHOICE) study is a prospective cohort study of patients who just started hemodialysis or peritoneal dialysis [44]. That study included 1,007 subjects, 98% of whom were enrolled in the study within 4 months. The study was started at a median of 45 days after the patients started dialysis. The results obtained 2.5 years later indicated that higher serum phosphate levels were an independent predictor of all-cause mortality. In addition, the relative risk of all-cause mortality was also high in subjects whose serum phosphate levels were high at the start of dialysis but decreased 6 months later. The abovementioned results suggest that the serum phosphate level at the start of dialysis is an important prognostic factor.

7.2. Vitamin D Receptor Activators (VDRAs)

Active vitamin D products inhibit PTH gene transcription and secretion as well as parathyroid cell proliferation in the parathyroid glands. Daily oral administration of 1α -(OH) D_3 (alfacalcidol), $1,25$ -(OH) $_2D_3$ (calcitriol), and/or $26,27$ -hexafluoro- $1,25$ -(OH) $_2D_3$ (falecalcitriol) is performed to prevent the progression of SHPT. However, the effect of this treatment is insufficient, because the expression of vitamin D receptor (VDR) decreases in uremia-associated parathyroid tumor.

A rapid increase in serum $1,25$ -(OH) $_2D$ levels due to intravenous administration of calcitriol can partly inhibit the synthesis and secretion of PTH in parathyroid cells, which express less VDR. Furthermore, $1,25$ -dihydroxy-22-oxavitamin D_3 (maxacalcitol, OCT), an analog in

which the carbon of calcitriol at position 22 is replaced with an oxygen atom, is characterized by a weaker intestinal calcium absorption capacity than that with the inhibition of PTH secretion. Therefore, it is unlikely to cause hypercalcemia.

Among the subjects in the ArMORR study who were not treated with active vitamin D analogs, 25OHD level, which exhibits individual nutritional vitamin D status, was elevated, while both all-cause mortality and CV mortality decreased (Figure 6). Furthermore, all-cause mortality and CV mortality decreased significantly in the subjects administered VDRA, regardless of 25OHD level, indicating that the prognosis of VDRA improved in the maintenance dialysis patients [45].

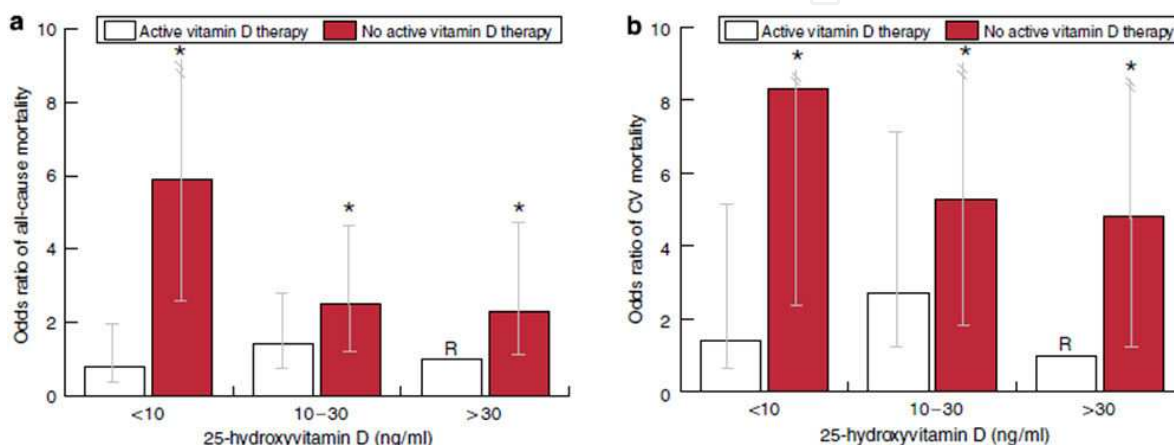


Figure 6. Multivariate-adjusted ORs of 90-day all-cause and cardiovascular (CV) mortality in the ArMORR study [45]. The ArMORR study involved 825 maintenance dialysis patients who were not treated with active vitamin D before or within 90 days of initiating dialysis to evaluate the effect of active vitamin D products on prognosis. 25OHD, which indicates the individual nutritional vitamin D status, was high in the subjects who were not treated with active vitamin D, while all-cause mortality and CV mortality decreased. Furthermore, all-cause mortality and CV mortality decreased significantly in the subjects administered with VDRA regardless of 25OHD levels.

7.3. Calcimimetics

Information on extracellular Ca^{2+} levels is transferred to parathyroid cells via CaR in the parathyroid glands, which control PTH secretion. Multivalent cations including Ca^{2+} , Mg^{2+} , and Gd^{3+} act on CaR as agonists. However, calcimimetics do not act as agonists but allosterically increase the sensitivity of CaR to multivalent cations [46].

Calcimimetic cinacalcet suppressed PTH secretion in cultured human pathological parathyroid cells obtained from primary hyperparathyroidism (PHPT) and SHPT patients, which exhibit reduced expression of CaR, the target molecule of cinacalcet [47]. These data support the clinical application of cinacalcet for PHPT and SHPT treatment.

Calcimimetic cinacalcet suppressed not only PTH secretion but also parathyroid cell proliferation, which prevented parathyroid hyperplasia *in vivo* in 5/6-nephrectomized rats, the animal model of SHPT [48]. Calcimimetic tecalcet also reversed the development of osteitis fibrosa in the SHPT rats [49]. In a relative hypocalcemic to normocalcemic environment, cal-

calcimimetics effectively suppress PTH secretion and parathyroid cell proliferation. Interestingly, cinacalcet suppressed aortic calcification in SHPT rats by decreasing serum PTH, calcium, and phosphate concentrations [50], suggesting that cinacalcet may be beneficial for the prevention of ectopic calcification as well as the improvement of morbidity and mortality in patients with CKD.

Cinacalcet also suppressed PTH secretion in *PTH-cyclin D1* transgenic mice [51]. *PTH-cyclin D1* transgenic mice are an animal model of PHPT that overexpress the *cyclin D1* oncogene in the parathyroid glands, which was accomplished by using a transgene that mimics the human *PTH-cyclin D1* gene rearrangement [52]. Tissue-specific overexpression of the *cyclin D1* oncogene not only resulted in abnormal parathyroid cell proliferation but, notably, also led to the development of biochemical hyperparathyroidism with characteristic bone abnormalities.

Hypercalcemia may stimulate considerable CaR activity, as the expression of CaR was suppressed in the parathyroid glands of these mice [52]. These conditions are compatible with the status observed in refractory SHPT patients undergoing maintenance hemodialysis. Although older transgenic mice exhibited advanced hyperparathyroidism caused by severely decreased CaR expression, cinacalcet suppressed both serum calcium and PTH concentrations [51] and parathyroid growth [53]. CaR is a potentially useful target for a therapeutic agent such as cinacalcet to suppress PTH secretion, despite the reduction in CaR expression observed in the parathyroid glands of patients with advanced PHPT and SHPT.

A meta-analysis of 8 randomized, double-blind, placebo-controlled trials (total number of subjects, 1,429) revealed that calcimimetics significantly decrease serum PTH, serum calcium, and serum phosphate levels, in turn significantly decreasing the serum calcium \times phosphate product [54] (Figure 7). The improvements in the abovementioned serum parameters due to calcimimetics were clarified in the analysis. However, no improvement in all-cause mortality or decreased parathyroidectomy was observed, and the incidence of bone fracture was not studied.

An observational study was performed using the United States Renal Data System to determine all-cause and CV mortality. Time-dependent Cox proportional hazards modeling found that all-cause and CV mortality rates were significantly reduced in cinacalcet-treated patients relative to those that did not receive cinacalcet treatment. Although this study revealed a significant survival benefit associated with cinacalcet, randomized clinical trials are needed to confirm a survival advantage associated with calcimimetics [55].

7.4. Percutaneous Ethanol Injection Therapy (PEIT)

Percutaneous ethanol injection therapy (PEIT) is performed by directly injecting ethanol into a parathyroid tumor under ultrasound guidance to necrotize parathyroid tumor cells. Its merits include minimal invasiveness and multiple sessions. However, the technique sometimes induces recurrent laryngeal nerve paralysis, making it inapplicable in the presence of recurrent laryngeal nerve paralysis in the contralateral parathyroid gland.

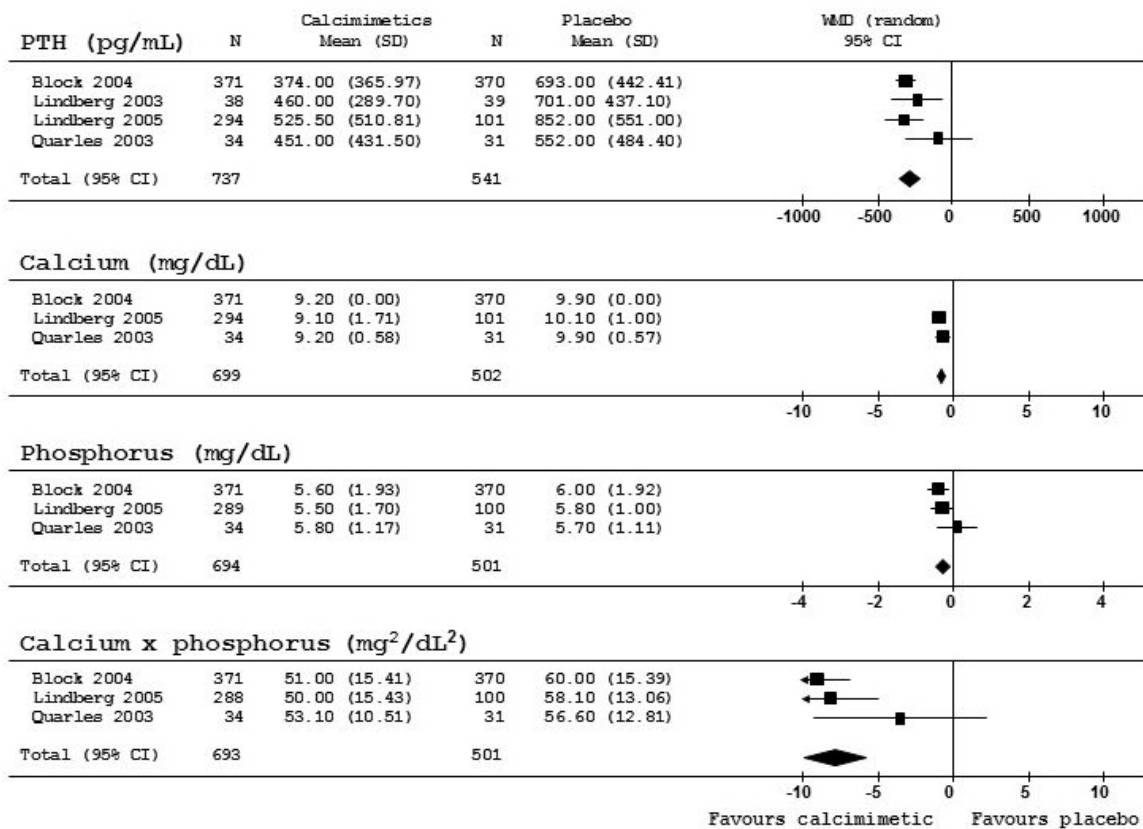


Figure 7. Positive effect of cinacalcet on serum parameters in the meta-analysis of 8 randomized, double-blind, placebo-controlled trials (total number of subjects, 1,429) [54] Cinacalcet significantly decreased serum PTH, calcium, and phosphate levels, thereby significantly decreasing the serum calcium x phosphate product; WMD: weighted mean difference, SD: standard deviation, CI: confidence interval

7.5. Parathyroidectomy (PTX)

PTX is recommended for the treatment of SHPT that is resistant to medical management. Isolation of the parathyroid glands always decreases serum PTH levels. However, there are often 5 or more parathyroid glands, and mediastinal or intrathyroid ectopic parathyroid tumors sometimes develop. Therefore, pre- and intraoperative detection of parathyroid glands is essential. The techniques for detecting them include subtotal extirpation, total extirpation, and total extirpation followed by autotransplantation.

8. Conclusion

Clinical evidence regarding CKD-MBD is reported in the literature, and guidelines have been developed accordingly. Well-controlled serum phosphate, calcium and PTH levels improve the prognosis of dialysis patients. Many pharmaceuticals aiming to achieve this goal have been developed and launched. As the pathology of CKD-MBD is elucidated, the prognosis of dialysis patients and their quality of life will improve.

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