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The effect of bone mineral metabolism disorder on cardiovascular events in uremia patients

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Abstract: *In patients with chronic renal insufficiency, mortality is higher in dialysis patients than in non-dialysis patients, and cardiovascular disease (CVD) is the leading cause of death [1]. Bone mineral metabolism disorder is a common complication in maintenance hemodialysis patients and a non-traditional risk factor for cardiovascular events [2]. Therefore, this paper reviews the pathological features, pathogenesis, risk factors, prevention, and treatment mechanisms of cardiovascular disease in patients with chronic kidney diseases-mineral and bone diseases, and discusses the evidence of the association of cardiovascular events in chronic kidney diseases-mineral and bone diseases. A recent study also reported a relationship between uremia, fractures, and cardiovascular events. The glomerular filtration rate is reduced in patients with chronic renal insufficiency, and disorders of bone mineral metabolism are increased, several mechanisms of which increase cardiovascular events in patients with chronic renal diseases - mineral and bone diseases. Ameliorating bone mineral metabolism disorders may be a potential future target for reducing cardiovascular events in patients with chronic kidney disease - mineral and bone disorders.*

Keywords: *maintenance hemodialysis; Bone mineral metabolism; Cardiovascular event*

1. Introduction

Patients with chronic kidney disease could be diagnosed with end-stage renal disease, if the estimated glomerular filtration rate (eGFR) < 15 mL /(min·1.73 m2). ESRD) is the uremia stage. Patients with ESRD should receive dialysis treatment when they have symptoms and signs of uremia. Maintenance hemodialysis is one of the kidney replacement methods in the treatment of uremia patients. It can not only remove metabolic waste in the patient's body but also maintain the balance of electrolytes, acid, and base and purify the blood.

chronic kidney disease -- mineral and bone disorder CKD-MBD was presented at the controversial KDIGO Conference on the definition, diagnosis, and classification of renal osteodystrophy in Madrid in 2005 [1]. CKD-MBD was defined at the meeting as a systemic disease involving the trinity of bone abnormalities, laboratory abnormalities, and vascular calcification, associated with serious outcomes such as fracture, cardiovascular morbidity, and mortality [1], [3] .

It is estimated that by 2040, CKD will be the fifth leading cause of death, with cardiovascular disease accounting for 20% of deaths in CKD [4]. Hemodialysis, uremia itself, abuse of calcium and phosphorus drugs, and other factors will lead to metabolic disorders of calcium and phosphorus, parathyroid, and other bone mineral elements, resulting in cardiovascular events [1] . In addition, the bone mineral components of uremia also contribute to cardiovascular events through their effects on blood pressure, activation of the renin-angiotensin-aldosterone system, vascular calcification, cardiac remodeling, and conduction. In an observational study of 38,935 patients with chronic renal insufficiency (CKD), Kwon, Y. E [5]et al. found that patients with chronic kidney disease (CKD) -- mineral and bone disorders suggest that weak bone and vascular disorders may be closely related in CKD patients. Fracture events were significantly associated with myocardial infarction (MI) in hemodialysis (HD) end-stage renal disease, especially vertebral fractures. Therefore, cardiovascular disease (CVD) is a serious complication of chronic kidney disease (CKD) [1; 3]. CKD is associated with atherosclerosis, arrhythmia, heart failure, and cardiac fibrosis. Therefore, CKD-MBD may be a direct and targeted cause of cardiovascular disease [2].

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In this review, we provide an overview of how these changes in bone mineral homeostasis relate to cardiovascular disease in patients with chronic renal insufficiency. There are many high-quality and comprehensive reviews in this field. In recent years, with the improvement of the understanding and diagnosis of CKD-MBD, CKD-MBD is considered to be one of the important non-traditional factors of CVD [6; 7]. The new treatment strategies aim not only to reduce circulating phosphate levels but also to maintain homeostasis between all mineral metabolic components and to avoid the cardiovascular effects of classical and non-classical mineral elements. The risk factors existing in CKD-MBD and the occurrence of CVD need further study. The study of the associated mechanisms will help to reduce the risk of cardiovascular events in patients with uremia.

2. Epidemiology of the association between CKD-MBD and CVD

Cardiovascular complications are the leading cause of death in patients with CKD, and the risk of cardiovascular death in dialysis patients is 10 to 30 times higher than in age, sex, and race-matched controls [8]. From a pathophysiological perspective, heart and kidney disease share many pathways, including inflammation and direct cellular immune-mediated mechanisms; Stress-mediated and hormonal responses; Metabolic and nutritional changes, including skeletal and mineral disturbances, hemodynamics, and changes in acid-base or fluid status; The development of anemia [4; 9]. Three main common mechanisms contribute to the development and acceleration of renal dysfunction -- cardiovascular disease-related mechanisms, hemodynamic mechanisms, and hormonal mechanisms [7]. The widespread effects of CKD on the cardiovascular system may reflect several pathophysiological mechanisms that link CKD to the development of CVD -- common risk factors (e.g., diabetes and hypertension), changes in bone mineral metabolism, anemia, volume overload, inflammation, and the presence of uremic toxins [9; 10].

3. Pathological characteristics and pathogenesis of CVD in CKD-MBD patients

3.1 Calcium and phosphorus, parathyroid hormone, and vitamin D lead to CVD

Calcium homeostasis is the hormonal regulation of serum ion calcium by parathyroid hormone, 1, 25-dihydroxy vitamin D, and serum ion calcium itself, which together regulate calcium transport in the intestine, kidney, and bone[11]. An observational study showed that patients with higher iPTH for calcium (≥300 pg/mL) had significantly higher all-cause mortality in the high calcium group than in the medium calcium group (IRR 1.99, 95% CI 1.16-3.42). All-cause mortality tended to be higher in the low-calcium group (aIRR 2.04, 95%CI 0.94-4.42) [12]. Inorganic phosphorus is an important element in the human body, which plays an important role in cell energy metabolism and cell signal transduction. Examples include adenosine and guanosine triphosphate (ATP, GTP), as well as the composition of phospholipid membranes and bones, which are building blocks of DNA and RNA. Blood phosphorus is equilibrated by Pi cotransporters coupled by NaPi-IIa and NaPi-IIc Na(+)- in the renal tubular epithelium, regulated by vitamin D, parathyroid hormone, fibroblast growth factor (FGF-23) and its co-receptor alpha-Klotho. The "tradeoff hypothesis" arises when the glomerular filtration rate decreases in CKD-MBD patients with decreased effective nephrons and high rates of cardiovascular disease and renal bone dystrophy in chronic renal failure (CRF) patients with hyperphosphatemia and calcium or parathyroid hormone (PTH) metabolism disorders[13]. Renal calcium and phosphorus excretion is disrupted, and phosphate retention and hyperphosphatemia are key factors in chronic kidney disease - mineral and bone disorders - in both kidney patients and the general population. Blood phosphorus is associated with endothelial dysfunction, and high blood phosphorus is associated with an elevated risk of all-cause cardiovascular death, cardiovascular events, and heart failure [7; 13]. Hyperphosphatemia is the key link in the progression of CKD-MBD. Prospective studies showed that an increase of 1 mg/dl in blood phosphorus was associated with a 26% increase in all-cause mortality and a 50% increase in CVD mortality[14]. When blood vessels are exposed to high phosphorus conditions in the body, they undergo apoptosis, transform into osteoid cells, and undergo extensive calcification [15], Therefore, hyperphosphatemia is associated with atherosclerosis, coronary artery calcification, and increased vessel wall thickness. Hyperphosphatemia plays a central role in initiating and driving many other disorders in CKD-MBD, such as increased concentrations of fibroblast growth factor 23, hypocalcemia, hypo vitamin D, and parathyroid hormone, which are also regulated concerning the increased risk of cardiovascular events [16].

The increase of PTH mainly comes from three ways: 1) Hyperphosphatemia stimulates

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calcium-sensitive receptors (CASRs) in the smooth muscle cells of the parathyroid gland, regulating the production of parathyroid hormone by regulating the synthesis and release of parathyroid hormone; 2) corticosteroid mediated calcium excretion in renal tubules, showing a tendency towards low calcium and low magnesium. The resulting secondary hyperparathyroidism leads to myocardial fibrosis and bone metabolism disorders.3). Direct stimulation of parathyroid glands by corticosteroids. Elevated PTH can lead to an increased risk of bone loss and fracture, coronary microvascular dysfunction, lipid and glucose metabolism disorders, subclinical aortic valve calcification, increased aortic sclerosis, endothelial dysfunction, and arterial hypertension through the renin-angiotensin-aldosterone system [12; 17]. Mortality was higher in the high iPTH group than in the medium iPTH group (IRR 1.65, 95% CI 1.39-1.96) [12]. PTH induces a "rapid response" encompassing ion regulatory channels and membrane signaling pathways through vitamin D receptor (VDR) and plasma membrane-associated VDRS to promote calcium increase in cardiomyocytes and further activate protein kinase C leading to myocardial hypertrophy [18]. A cross-sectional study showed that FGF-23, iPTH, and IL-6 are determinants of valve calcification during regular hemodialysis in CKD-MBD patients [22]. In vivo, PTH can also act on the MEK/ERK pathway to promote cardiomyocyte hypertrophy and further affect cardiac function [19; 20]. In addition, Jeong, S [21] et al. found that MicroRNAs, as biomarkers of bone biology, play a role in protein degradation and proteolysis related to parathyroid hormone and parathyroid hormone. It is suggested that the dynamic relationship between MicroRNAs, parathyroid hormone, and renal bone disease remains to be further studied. A cross-sectional study showed that age, systolic and diastolic blood pressure (DBP), hypersensitive C-reactive protein (HsCRP) levels, mean iPTH, and SD iPTH were significantly higher in patients who died, while albumin levels, SI iPTH and SI Ca were significantly lower in patients who survived. Multivariate analysis showed that age, low albumin, high diastolic blood pressure, SI iPTH, and SI Ca were independent predictors of cardiac death [22].

Vitamin D also works with parathyroid hormone, calcitonin, and fibroblast growth factor-23 to regulate serum calcium and phosphorus levels [23]. Vitamin D not only increases the absorption of calcium and phosphate in the gut but also promotes reabsorption by the kidneys, resulting in elevated serum calcium and phosphate levels [24; 25]. Low serum 25 hydroxyvitamin D (25[OH]2D) levels were positively correlated with glomerular filtration rate and negatively correlated with serum parathyroid gland (PTH) levels. With the gradual loss of renal function in CKD-MBD patients, 1α-hydroxylase inhibitors increase (e.g. Fibroblast Growth Factor-23 (FGF-23)), resulting in reduced 1α-hydroxylase synthesis and deficiency of 1,25 (OH) 2D. Vitamin D receptor deficiency inhibits the renin-angiotensin system by inducing activation of the renin-angiotensin system by down-regulating the silence-message regulatory factor (SIRT1) in podocytes [23].In a human cross-sectional study, Dong, J[24] et al found that calcitriol treatment reduced the expression of AT(1)R, NOX-2, NOX-4, and p67(phlox), and increased the expression of superoxide dismutase (SOD)-1, thus reducing the inflammatory response and protecting endothelial cells. And the lower the level of vitamin D, the higher the level of plasma renin activity (PRA), the higher the concentration of angiotensin-ii (Ang-II), and the higher the activity of renin-angiotensin system in vascular tissues [32]. Therefore, public health needs to evaluate whether the treatment of vitamin D deficiency can prevent premature death.

3.2 Fibroblast growth factor-23-Klotho axis

Fibroblast growth factor 23 (FGF23), a hormone secreted by bone cells discovered in the last 10 years, plays an important role in phosphate metabolism [26]. High phosphorus can stimulate the secretion of FGF-23 from bone cells [27], Increased levels of FGF-23 are associated with an increased risk of death in patients with chronic kidney disease [28]. Klotho is widely expressed in vivo as a co-receptor for a fibroblast growth factor (FGF), but its levels are highest in the kidney [[29]], So kidneys are the main source of the anti-aging protein klotho. Studies have shown that intramuscular injection of FGF-23 can cause left ventricular hypertrophy, suggesting that FGF-23 has a direct effect on the heart [30]. In addition, FGF-23 has been reported to specifically activate FGFR-4 on cardiomyocytes to stimulate activated T cell signaling phospholipase C(PLC)γ, leading to a series of pathological processes such as cardiac hypertrophy and LVH, which disappear when FGFR-4 is specifically knocked out. Therefore, the FGF23/FGFR4/PLCγ pathway is involved in LVH and mechanical and electrical dysfunction [31]. Three main mechanisms are thought to contribute to CKD-LVH: afterload and preload-related factors as well. non-afterload, non-preload related factors[32].However, in an observational study by Takashi, Y[33]., serum FGF23 concentration was independently associated with serum calcium and phosphorus concentrations ($\beta = 0.276$, $p < 0.001$; $\beta = 0.689$, $p < 0.001$). Therefore, further randomized controlled trials are needed to verify the relationship between serum FGF23 concentration and cardiac dysfunction, atherosclerosis, infection, and systemic inflammation. In

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addition, exogenous FGF-23 and klotho proteins inhibited LVH, and PLCγ signals were not activated, while extracellular regulated protein kinases and ERK signal activity increased significantly. These results indicate that the FGF23/ ERK signaling pathway is preferentially activated if the exogenous klotho protein is supplemented. In the absence of klotho protein, FGF23/FGFR4/PLCγ pathway can promote LVH generation, thus klotho protein can inhibit the direct cardiac toxicity of FGF23 [19], This provides a new direction for future treatment. FGF-23 maintains its receptor resistance through a positive feedback loop characterized by direct downregulation of klotho expression [[28; 34]], However, Kloth protein is positively correlated with eGRFR, so FGF-23 is an independent correlation factor for ventricular remodeling in patients with CKD, and FGF-23 is significantly correlated with cardiovascular mortality and all-cause mortality [38]. However, studies have shown that even if serum phosphate levels are in the normal range, FGF-23 remains one of the most important predictors of death in CKD [28].

3.3 Enhanced bone metabolism

Bone fragility is not only affected by low bone volume and mass, but also by poor microstructure and tissue quality. Transiliac ridge bone biopsy can diagnose osteoporosis without the exclusion of other kidney-related bone diseases, but its availability is limited, and new techniques such as bone trabecular scoring and high-resolution imaging studies can be used to better assess bone quality and fracture risk in patients with CKD [35]. Fracture probability is increased in dialysis patients due to mineral metabolism disorder, and bone mineral conversion disorder is a common complication in patients with renal impairment. In addition to increasing the risk of cardiovascular disease, they also promote bone diseases such as osteoporosis, bone pain, and fractures. The brittle fracture approach in patients with stage 1 to 3a CKD may be similar to that in the general population. However, in stage 3b-5, World Health Organization (WHO) criteria based on bone mineral density (BMD) or fragility fractures do not identify osteoporosis because fractures can occur with low bone density [[36]]. It is currently believed that the higher degree of vascular calcification in patients with low transforming osteopathy is related to the reduced buffering ability of bone tissue against calcium and phosphorus metabolism disorders in low transforming osteopathy [37].

3.4 Ectopic calcification of soft tissue

Elevated parathyroid hormone levels in patients with decreased renal function are associated with soft tissue calcification and subsequent adverse CVD outcomes [38].

It was previously thought that ectopic Vascular calcification in CKD was the result of the passive deposition of calcium and phosphorus, but it is now believed that vascular calcification is an active regulation, the central link of which is the transdifferentiation of Vascular smooth muscle cells (VSMC) into cartilage or osteoblast cells under certain stimulation conditions. Bone and blood vessel mineralization share a common pathway, a multifaceted endocrine tandem between the bone and arterial system, a relationship known as the "calcification paradox" [39]. A CKD-MBD rat model was established to observe the pathophysiological phenotype of the bone-vascular axis. It was found that with calcium deposition in the abdominal aorta of CKD-MBD rats, aortic RNA sequencing showed that the level of the inositol receptor 2 (ITPR2) gene in CKD-MBD rats decreased significantly. The results showed that the trabecular microstructure of femur bone in CKD-MBD rats deteriorated and alveolar bone loss worsened[40]. It is suggested that ITPR2 may be a potential target of the bone-vascular axis in CKD-MBD. Calcification of central vessels was evident in hyperphosphatemia rats and mice, and high phosphorus was the main factor promoting the transformation of VSMC into osteoblasts [19; 41], For every 1mg/dl increase in blood phosphorus, aortic calcification increased by 25%, coronary artery calcification by 21%, and mitral valve calcification by 62% [42], Meanwhile, hyperphosphatemia increased the activity of sodium-dependent cotransporters PiT-1 and PiT-2, which up-regulated genes associated with matrix mineralization [20], therefore, PTH can increase cardiovascular calcification. At the later stage of CKD, serum parathyroid hormone levels can overcome peripheral resistance to bone formation inhibitors such as parathyroid hormone and exacerbate high turnover bone disease [43; 44]. Passive deposition of calcium and phosphate in soft tissues in secondary hyperparathyroidism and hyperphosphatemia and the active role of inorganic phosphate in the vascular system of these patients by directly inducing extraosseous mineralization of the medium lead to increased cardiovascular mortality in patients with uremia [45; 46]. It was found that the use of over-recommended doses of PTH resulted in a significant increase in the expression of inflammatory factor IL-6 and glycosylated end-product receptors in endothelial cells, thus promoting atherosclerotic plaque formation and

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vascular calcification [16].In addition, biomarkers of VC -- namely phosphate, fibroblasts growth factor 23 (FGF23), osteopontin (OPN), osteoprotegerin (OPG), matrix Gla protein, and fetoglobulin A-all, which have been considered major participants of VC in vitro or animal model experimental studies [2; 3; 20]. Ye, Y et al. found that iron death of vascular smooth muscle cells (VSMCs) promotes vascular calcification in CKD by inhibiting the SLC7A11/GSH/GPX4 axis, providing a new targeting strategy for vascular calcification. There have been inconsistent reports on the biomedical effects of FGF23 on vascular calcification, and increasing evidence supports the favorable protective effect of alpha-Klotho on vascular calcification [29; 31]. Zaloszyc, A [47]et al., found in mice that osteoblast-specific Gα(q/11) deletion (KO) mice on an increased high-phosphorus diet reduced the thickness and area of metaphyseal and metaphysis cortex, as well as the number of trabeculae, further exacerbating the mineral bone disease.

4. Related Treatment

CKD-MBD is an important non-traditional factor of CVD. Active control of the progression of CKD-MBD improves survival and reduces cardiovascular events. Control blood calcium, phosphorus, and parathyroid hormone levels with diet, drugs, or blood purification; To correct lipid metabolism disorder and chronic inflammatory response; Increase the types and number of intestinal probiotics to reduce the production of uremic toxins; Maintain adequate dialysis; Parathyroidectomy or partial resection is performed if necessary.

4.1 Control calcium and phosphorus balance

Phosphorus is found in most foods, especially from proteins, phytates, and food additives. A very low protein diet without animal protein (0.3 g/kg body weight per day) significantly reduced serum phosphorus levels and serum FGF23 levels compared with a low protein diet with animal and plant foods as protein sources (0.6 g/kg body weight per day) [48]. According to the K/DOQI guidelines, blood phosphorus should be strictly controlled at 3.5 ~ 5.5mg/dl, blood calcium should be controlled at the standard level of 8.4 ~ 9.5mg/dl, parathyroid hormone level should be maintained at 2-9 times the upper limit of normal, the target is 150-300 pg/mL, and the product of calcium and phosphorus should be kept < 55mg2 / dl2. The recommended daily limit of phosphorus is 800 to 1000mg per day [1; 49] .

Since diet and dialysis are often insufficient to control serum phosphorus levels, many patients need to be treated with phosphorus binders. Current studies have shown that early use of phosphorus binders can improve long-term survival in patients with CKD. In Fang, Y [50]because diet and dialysis are often insufficient to control serum phosphorus levels, many patients need to be treated with phosphorus binders. Current studies have shown that early use of phosphorus binders can improve long-term survival in patients with CKD. In a rat model of diabetic kidney injury, treatment with medium phosphorus binder restored plasma fibroblast growth fact-23 levels but did not affect vascular calcification or bone dystrophy. In CKD-2 mice, administration of monoclonal antibody and circulating Dickkopf-1 after kidney injury stimulated bone formation rate and corrected bone dystrophy. And prevent vascular calcification stimulated by CKD.

Phosphorus binding agents that do not contain aluminum and calcium, such as lanthanum carbonate and Svilam, are more suitable for patients with hypercalcemia, which can reduce the product of blood phosphorus and calcium phosphorus, to delay the occurrence and development of ectopic vascular calcification. Compared with calcium carbonate and calcium acetate, lanthanum carbonate-induced bone turnover inhibition is lower and may improve systolic function and heart size compared with calcium carbonate [51]. A prospective study by Ohtake, T [46]et al showed that lanthanum carbonate significantly delayed the progression of CAC in HD patients. The absence of Calcium-sensing receptor (CaSR) expression in vascular smooth muscle cells exacerbates in vitro vascular calcification. In contrast, calcifiers reduce vascular calcification and act as allosteric activators of CaSR, but no reduction in cardiovascular events was observed in patients with CKD who were randomized to receive calcium compared with a placebo in a trial to reduce cardiovascular events [52]. In a prospective trial, Etelcalcetide, a novel calcium-like agent, reduced serum calcium and phosphorus levels in patients with end-stage renal disease (ESRD) undergoing hemodialysis (HD) at the end of the study. In the death structure, the proportion of CV events was more than 70% higher in the conventional treatment group than in the eticartide treatment group. 69.2% and 40.0%, respectively. The proportion of patients requiring parathyroidectomy in the historical group was significantly more than 3 times that in the traditional treatment group ($P < 0.05$) [53]. In addition, parathyroidectomy or partial excision, if

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necessary, can also correct calcium and phosphorus disorders.

Adequate hemodialysis is an important means to control the balance of calcium and phosphorus. Uremic toxins are classified according to their physicochemical properties into the following categories: free water-soluble low molecular weight solutes (500 Dalton), protein-bound solutes, and intermediates (≥500 Dalton) . In general, small water-soluble molecules with molecular weights of < 500 Dalton, such as urea and sodium, can be efficiently and easily covered by most filters. However, PTH is a medium-sized uremic toxin that cannot be cleared by routine dialysis. The existing polysaccharide-based multilayer adsorption can increase urinary toxin excretion better than the traditional layer-by-layer (LBL) adsorption, and reduce protein adsorption, platelet adhesion, and thrombosis based on heparin fixation [54].

There is evidence that calcium mass balance is positive when using dialysate calcium concentration (DCa)Ca 3.5 mEq/L, negative or neutral when using DCa 2.5 mEq/L, and positive or negative when using DCa 3.0 mEq/L. Overall, DCa use of 2.5 mEq/L was generally associated with elevated blood calcium levels, lower serum PTH levels, and the use of lower doses of vitamin D analogs, while lower DCa use was generally associated with the opposite effect.

4.2 VD and its Derivatives: Vitamin D receptor agonist (VDRA)

Vitamin D refers to a group of fat-soluble, steroid compounds that are essential for intestinal absorption and the regulation of calcium and phosphate metabolism. Most clinicians refer to Endocrine Society recommendations, where 25 (OH) D concentrations < 20 ng/mL are defined as inadequate, concentrations between 21 and 29 ng/mL are defined as inadequate, and serum levels > 30 ng/mL are defined as normal or adequate. Progressive parathyroid hormone or persistently high levels in non-dialysis patients in stages CKD3 to 5a should be corrected for vitamin D deficiency. Vitamin D can reduce the PTH of CKD-MBD patients by 31.5 pg/mL, and reduce the occurrence of hypercalcemia and hyperphosphatemia [55]. Studies have found that a therapeutic dose of 25 (OH) D can effectively inhibit the occurrence of calcification, but a high dose can promote vascular calcification [56]. Swart, KM[57] et al showed that vitamin D supplementation did not affect blood pressure and HbA1c primary outcomes. And no clinical trials have shown that these therapies reduce cardiovascular events or mortality. Combined vitamin D and calcium supplementation significantly reduced the incidence of fracture, RR = 0.859 (95%CI 0.741-0.996; P =.045, I = 25.48) [58]. In addition, Vitamin D receptor agonist (VDRA) is a widespread ligand-activated nuclear transcription factor with selective and non-selective types. Common clinical non-selective VDRA mainly include facial and calcitriol, etc. Selective VDRA mainly includes calcium petrol, tamarin, fluoride, theocalcitol, etc. Its price is relatively expensive. Dong, J[59]et al. 's in vitro experiments showed that calcitriol improved endothelial function by normalizing the expression of free radical scavenging enzymes, thereby preventing excessive production of oxidative stress and protecting renal vascular function in hypertension. Selective VDRA mainly targets parathyroid cells, the gastrointestinal tract, and bone tissue, and has the strongest effect on parathyroid cells, so its high calcium and high phosphorus side effects are less. VDRA can directly act on vascular smooth muscle cells to promote osteoblast changes, but at the same time inhibit the above effects through the FGF23-Klotho pathway[60]. Therefore, it is believed that VDRA is independent of changes in blood calcium and phosphorus, and has a bidirectional effect. The exact mechanism of action needs closer clinical follow-up and study.

4.3 New Drugs

Some of the most common treatments for CKD, such as vitamin K antagonists -- warfarin, calcifiers, and phosphate binders -- may have adverse effects on vitamin K metabolism and storage in patients with CKD. In addition, the majority of hemodialysis patients due to uremic toxins lead to intestinal flora disorders, manifested as subclinical vitamin K deficiency. Three forms of vitamin K are known: vitamin K1 (phylloquinone), vitamin K2 (methyl naphthoquinone), and vitamin K3 (naphthoquinone), of which vitamin k2 is synthesized primarily by the gut microbiome [61]. Vitamin K as a coenzyme of Y-glutamine carboxylase converts carboxylated vitamin K-dependent protein to incomplete carboxylation. In addition, it activates the expression of genes encoding proteins involved in maintaining bone mass and rebuilding bone by binding to nuclear steroids and foreign receptors [62]. Recent in vitro studies have shown that vitamin K2 promotes osteogenic differentiation through the Bcl-6/STAT axis and IL-6/JAK/STAT signaling pathway [63]. In addition, a study in a rat model showed that the combination of a high-vitamin k2 diet and phosphate binders significantly reduced vascular calcification compared to treatment with vitamin K2 or phosphate binders alone [64].

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5. Look ahead

CKDMBD has intricate mechanisms from any point of view, among which the occurrence of cardiovascular events is the most important link. This interdisciplinary approach requires two-way professional interaction among various majors and forms new cooperative relationships. In addition, widespread improvements in the diagnosis of MBDS will also change our ability to study and treat their potential impact on cardiovascular disease.

References

[1] T. Isakova, T.L. Nickolas, M. Denburg, S. Yarlagadda, D.E. Weiner, O.M. Gutierrez, V. Bansal, S.E. Rosas, S. Nigwekar, J. Yee, and H. Kramer, KDOQI US Commentary on the 2017 KDIGO Clinical Practice Guideline Update for the Diagnosis, Evaluation, Prevention, and Treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD). Am J Kidney Dis 70 (2017) 737-751.

[2] J. Lunyera, and J.J. Scialla, Update on Chronic Kidney Disease Mineral and Bone Disorder in Cardiovascular Disease. Semin Nephrol 38 (2018) 542-558.

[3] R. Vanholder, Z. Massy, A. Argiles, G. Spasovski, F. Verbeke, N. Lameire, and G. European Uremic Toxin Work, Chronic kidney disease as cause of cardiovascular morbidity and mortality. Nephrol Dial Transplant 20 (2005) 1048-56.

[4] H. Fujii, [CKD-MBD and cardiovascular disease.]. Clin Calcium 29 (2019) 179-184.

[5] Y.E. Kwon, H.Y. Choi, H.J. Oh, S.Y. Ahn, D.R. Ryu, and Y.J. Kwon, Vertebral fracture is associated with myocardial infarction in incident hemodialysis patients: a Korean nationwide population-based study. Osteoporos Int 31 (2020) 1965-1973.

[6] D.E. Weiner, H. Tighiouart, E.F. Elsayed, J.L. Griffith, D.N. Salem, A.S. Levey, and M.J. Sarnak, The Framingham predictive instrument in chronic kidney disease. J Am Coll Cardiol 50 (2007) 217-24.

[7] J. Jankowski, J. Floege, D. Fliser, M. Böhm, and N. Marx, Cardiovascular Disease in Chronic Kidney Disease: Pathophysiological Insights and Therapeutic Options. Circulation 143 (2021) 1157-1172.

[8] L. Di Micco, G.R. Mozzillo, and B. Cianciaruso, [Epidemiology of cardiovascular disease in CKD-MBD]. G Ital Nefrol 26 Suppl 49 (2009) S3-10.

[9] J.C. Schefold, G. Filippatos, G. Hasenfuss, S.D. Anker, and S. von Haehling, Heart failure and kidney dysfunction: epidemiology, mechanisms and management. Nat Rev Nephrol 12 (2016) 610-23.

[10] K. Matsushita, S.H. Ballew, A.Y. Wang, R. Kalyesubula, E. Schaeffner, and R. Agarwal, Epidemiology and risk of cardiovascular disease in populations with chronic kidney disease. Nat Rev Nephrol 18 (2022) 696-707.

[11] M. Ruospo, S.C. Palmer, P. Natale, J.C. Craig, M. Vecchio, G.J. Elder, and G.F. Strippoli, Phosphate binders for preventing and treating chronic kidney disease-mineral and bone disorder (CKD-MBD). Cochrane Database Syst Rev 8 (2018) Cd006023.

[12] S. Asada, K. Yokoyama, C. Miyakoshi, S. Fukuma, Y. Endo, M. Wada, T. Nomura, Y. Onishi, M. Fukagawa, S. Fukuhara, and T. Akizawa, Relationship between serum calcium or phosphate levels and mortality stratified by parathyroid hormone level: an analysis from the MBD-5D study. Clin Exp Nephrol 24 (2020) 630-637.

[13] S. Lee, and S.J. Kim, Effects of Normal Reference Range of Phosphorus and Corresponding PTH on Endothelial Function in CKD Patients. Front Med (Lausanne) 9 (2022) 935977.

[14] M.M. Popovtzer, W.F. Pinggera, M.P. Hutt, J. Robinette, C.G. Halgrimson, and T.E. Starzl, Serum parathyroid hormone levels and renal handling of phosphorus in patients with chronic renal disease. J Clin Endocrinol Metab 35 (1972) 213-8.

[15] R. Shroff, Phosphate is a vascular toxin. Pediatr Nephrol 28 (2013) 583-93.

[16] A. Galassi, A. Cupisti, A. Santoro, and M. Cozzolino, Phosphate balance in ESRD: diet, dialysis and binders against the low evident masked pool. J Nephrol 28 (2015) 415-29.

[17] K. Kono, H. Fujii, K. Watanabe, S. Goto, and S. Nishi, Relationship between parathyroid hormone and renin-angiotensin-aldosterone system in hemodialysis patients with secondary hyperparathyroidism. J Bone Miner Metab 39 (2021) 230-236.

[18] O. Gutierrez, T. Isakova, E. Rhee, A. Shah, J. Holmes, G. Collerone, H. Juppner, and M. Wolf, Fibroblast growth factor-23 mitigates hyperphosphatemia but accentuates calcitriol deficiency in chronic kidney disease. J Am Soc Nephrol 16 (2005) 2205-15.

[19] J.A. Navarro-Garcia, M. Fernandez-Velasco, C. Delgado, J.F. Delgado, O.M. Kuro, L.M. Ruilope, and G. Ruiz-Hurtado, PTH, vitamin D, and the FGF-23-klotho axis and heart: Going beyond the confines of nephrology. Eur J Clin Invest 48 (2018).

ISSN 2618-1584 Vol. 5, Issue 3: 29-38, DOI: 10.25236/FMSR.2023.050305

[20] S. Liabeuf, H. Okazaki, L. Desjardins, D. Fliser, D. Goldsmith, A. Covic, A. Wiecek, A. Ortiz, A. Martinez-Castelao, B. Lindholm, G. Suleymanlar, F. Mallamaci, C. Zoccali, G. London, and Z.A. Massy, Vascular calcification in chronic kidney disease: are biomarkers useful for probing the pathobiology and the health risks of this process in the clinical scenario? Nephrol Dial Transplant 29 (2014) 1275-84.

[21] S. Jeong, J.M. Oh, K.H. Oh, and I.W. Kim, Differentially expressed miR-3680-5p is associated with parathyroid hormone regulation in peritoneal dialysis patients. PLoS One 12 (2017) e0170535.

[22] S. Ulusoy, G. Ozkan, B. Guvercin, and A. Yavuz, The Relation Between Variability of Intact Parathyroid Hormone, Calcium, and Cardiac Mortality in Hemodialysis Patients. Artif Organs 40 (2016) 1078-1085.

[23] G. Cianciolo, M. Cappuccilli, F. Tondolo, L. Gasperoni, F. Zappulo, S. Barbuto, F. Iacovella, D. Conte, I. Capelli, and G. La Manna, Vitamin D Effects on Bone Homeostasis and Cardiovascular System in Patients with Chronic Kidney Disease and Renal Transplant Recipients. Nutrients 13 (2021).

[24] N.S. Akimbekov, I. Digel, D.K. Sherelkhan, and M.S. Razzaque, Vitamin D and Phosphate Interactions in Health and Disease. Adv Exp Med Biol 1362 (2022) 37-46.

[25] G. Rashid, J. Bernheim, J. Green, and S. Benchetrit, Parathyroid hormone stimulates the endothelial nitric oxide synthase through protein kinase A and C pathways. Nephrol Dial Transplant 22 (2007) 2831-7.

[26] T. Shimada, Y. Yamazaki, M. Takahashi, H. Hasegawa, I. Urakawa, T. Oshima, K. Ono, M. Kakitani, K. Tomizuka, T. Fujita, S. Fukumoto, and T. Yamashita, Vitamin D receptor-independent FGF23 actions in regulating phosphate and vitamin D metabolism. Am J Physiol Renal Physiol 289 (2005) F1088-95.

[27] P.A. Ureña Torres, J.C. Souberbielle, and M.C. Solal, Bone Fragility in Chronic Kidney Disease Stage 3 to 5: The Use of Vitamin D Supplementation. Metabolites 12 (2022).

[28] L. Gan, and Q. Zhou, [Correlations of FGF23 and Klotho with cardiovascular injury in chronic kidney disease patients]. Zhong Nan Da Xue Xue Bao Yi Xue Ban 42 (2017) 1058-1065.

[29] S. Yamada, and C.M. Giachelli, Vascular calcification in CKD-MBD: Roles for phosphate, FGF23, and Klotho. Bone 100 (2017) 87-93.

[30] C. Faul, A.P. Amaral, B. Oskouei, M.C. Hu, A. Sloan, T. Isakova, O.M. Gutierrez, R. Aguillon-Prada, J. Lincoln, J.M. Hare, P. Mundel, A. Morales, J. Scialla, M. Fischer, E.Z. Soliman, J. Chen, A.S. Go, S.E. Rosas, L. Nessel, R.R. Townsend, H.I. Feldman, M. St John Sutton, A. Ojo, C. Gadegbeku, G.S. Di Marco, S. Reuter, D. Kentrup, K. Tiemann, M. Brand, J.A. Hill, O.W. Moe, O.M. Kuro, J.W. Kusek, M.G. Keane, and M. Wolf, FGF23 induces left ventricular hypertrophy. J Clin Invest 121 (2011) 4393-408.

[31] A. Grabner, A.P. Amaral, K. Schramm, S. Singh, A. Sloan, C. Yanucil, J. Li, L.A. Shehadeh, J.M. Hare, V. David, A. Martin, A. Fornoni, G.S. Di Marco, D. Kentrup, S. Reuter, A.B. Mayer, H. Pavenstadt, J. Stypmann, C. Kuhn, S. Hille, N. Frey, M. Leifheit-Nestler, B. Richter, D. Haffner, R. Abraham, J. Bange, B. Sperl, A. Ullrich, M. Brand, M. Wolf, and C. Faul, Activation of Cardiac Fibroblast Growth Factor Receptor 4 Causes Left Ventricular Hypertrophy. Cell Metab 22 (2015) 1020-32.

[32] R.J. Glassock, R. Pecoits-Filho, and S.H. Barberato, Left ventricular mass in chronic kidney disease and ESRD. Clin J Am Soc Nephrol 4 Suppl 1 (2009) S79-91.

[33] Y. Takashi, S. Wakino, H. Minakuchi, M. Ishizu, A. Kuroda, H. Shima, M. Tashiro, K. Miya, K. Okada, J. Minakuchi, S. Kawashima, M. Matsuhisa, T. Matsumoto, and S. Fukumoto, Circulating FGF23 is not associated with cardiac dysfunction, atherosclerosis, infection or inflammation in hemodialysis patients. J Bone Miner Metab 38 (2020) 70-77.

[34] X. Lu, and M.C. Hu, Klotho/FGF23 Axis in Chronic Kidney Disease and Cardiovascular Disease. Kidney Dis (Basel) 3 (2017) 15-23.

[35] K. Asadipooya, M. Abdalbary, Y. Ahmad, E. Kakani, M.C. Monier-Faugere, and A. El-Husseini, Bone Quality in CKD Patients: Current Concepts and Future Directions - Part I. Kidney Dis (Basel) 7 (2021) 268-277.

[36] F. Aguiar, C. Meng, L. Pereira, I. Brito, and J.M. Frazão, Bone biopsy: an ally in the management of fragility fractures in chronic kidney disease. Acta Reumatol Port 43 (2018) 201-209.

[37] A. Sidibé, D. Auguste, L.C. Desbiens, C. Fortier, Y.P. Wang, S. Jean, L. Moore, and F. Mac-Way, Fracture Risk in Dialysis and Kidney Transplanted Patients: A Systematic Review. JBMR Plus 3 (2019) 45-55.

[38] S. Lee, H.J. Chung, S. Jung, H.N. Jang, S.H. Chang, H.J. Kim, and M.C. Cho, 24,25-Dihydroxy Vitamin D and Vitamin D Metabolite Ratio as Biomarkers of Vitamin D in Chronic Kidney Disease. Nutrients 15 (2023).

[39] V. Persy, and P. D'Haese, Vascular calcification and bone disease: the calcification paradox.

ISSN 2618-1584 Vol. 5, Issue 3: 29-38, DOI: 10.25236/FMSR.2023.050305

Trends Mol Med 15 (2009) 405-16.
[40] Q. Xiao, Y. Tang, H. Luo, S. Chen, Q. Tang, R. Chen, L. Xiong, J. Xiao, D. Hong, L. Wang, G. Li, and Y. Li, Inositol 1,4,5-trisphosphate receptor type 2 is associated with the bone-vessel axis in chronic kidney disease-mineral bone disorder. Ren Fail 45 (2023) 2162419.
[41] P. Ureña-Torres, L. D'Marco, P. Raggi, X. García-Moll, V. Brandenburg, S. Mazzaferro, A. Lieber, L. Guirado, and J. Bover, Valvular heart disease and calcification in CKD: more common than appreciated. Nephrol Dial Transplant 35 (2020) 2046-2053.
[42] S.C. Palmer, A. Teixeira-Pinto, V. Saglimbene, J.C. Craig, P. Macaskill, M. Tonelli, G. de Berardis, M. Ruospo, and G.F. Strippoli, Association of Drug Effects on Serum Parathyroid Hormone, Phosphorus, and Calcium Levels With Mortality in CKD: A Meta-analysis. Am J Kidney Dis 66 (2015) 962-71.
[43] Y.C. Hou, C.M. Zheng, H.W. Chiu, W.C. Liu, K.C. Lu, and C.L. Lu, Role of Calcimimetics in Treating Bone and Mineral Disorders Related to Chronic Kidney Disease. Pharmaceuticals (Basel) 15 (2022).
[44] K. Nitta, T. Ogawa, N. Hanafusa, and K. Tsuchiya, Recent Advances in the Management of Vascular Calcification in Patients with End-Stage Renal Disease. Contrib Nephrol 198 (2019) 62-72.
[45] M. Cozzolino, M. Gallieni, G. Chiarelli, and D. Brancaccio, Calcium and phosphate handling in peritoneal dialysis. Contrib Nephrol 150 (2006) 214-225.
[46] T. Ohtake, S. Kobayashi, M. Oka, R. Furuya, M. Iwagami, D. Tsutsumi, Y. Mochida, K. Maesato, K. Ishioka, H. Moriya, and S. Hidaka, Lanthanum carbonate delays progression of coronary artery calcification compared with calcium-based phosphate binders in patients on hemodialysis: a pilot study. J Cardiovasc Pharmacol Ther 18 (2013) 439-46.
[47] A. Zaloszyc, P. Choquet, A. Sayeh, M. Bartosova, B. Schaefer, U. Huegel, G. Aubertin-Kirch, C. Healy, F. Severac, S. Rizzo, G. Boivin, F. Schaefer, M. Fischbach, J. Bacchetta, S. Bahram, and C.P. Schmitt, Inactivation of Osteoblast PKC Signaling Reduces Cortical Bone Mass and Density and Aggravates Renal Osteodystrophy in Mice with Chronic Kidney Disease on High Phosphate Diet. Int J Mol Sci 23 (2022).
[48] Y. Taketani, F. Koiwa, and K. Yokoyama, Management of phosphorus load in CKD patients. Clin Exp Nephrol 21 (2017) 27-36.
[49] K. Yoshida, T. Mizukami, M. Fukagawa, T. Akizawa, H. Morohoshi, T. Sambe, H. Ito, H. Ogata, and N. Uchida, Target phosphate and calcium levels in patients undergoing hemodialysis: a post-hoc analysis of the LANDMARK study. Clin Exp Nephrol 27 (2023) 179-187.
[50] Y. Fang, C. Ginsberg, M. Seifert, O. Agapova, T. Sugatani, T.C. Register, B.I. Freedman, M.C. Monier-Faugere, H. Malluche, and K.A. Hruska, CKD-induced wingless/integration1 inhibitors and phosphorus cause the CKD-mineral and bone disorder. J Am Soc Nephrol 25 (2014) 1760-73.
[51] V. Cernaro, S. Calimeri, A. Laudani, and D. Santoro, Clinical Evaluation of the Safety, Efficacy and Tolerability of Lanthanum Carbonate in the Management of Hyperphosphatemia in Patients with End-Stage Renal Disease. Ther Clin Risk Manag 16 (2020) 871-880.
[52] R. Shroff, D.A. Long, and C. Shanahan, Mechanistic insights into vascular calcification in CKD. J Am Soc Nephrol 24 (2013) 179-89.
[53] I. Dudar, I. Shifris, S. Dudar, and V. Kulish, Current therapeutic options for the treatment of secondary hyperparathyroidism in end-stage renal disease patients treated with hemodialysis: a 12-month comparative study. Pol Merkur Lekarski 50 (2022) 294-298.
[54] R.S. Juang, X. Su, and I.C. Lee, Feasibility Assessment of Parathyroid Hormone Adsorption by Using Polysaccharide-Based Multilayer Film Systems. Polymers (Basel) 13 (2021).
[55] M.C. Mann, A.J. Hobbs, B.R. Hemmelgarn, D.J. Roberts, S.B. Ahmed, and D.M. Rabi, Effect of oral vitamin D analogs on mortality and cardiovascular outcomes among adults with chronic kidney disease: a meta-analysis. Clin Kidney J 8 (2015) 41-8.
[56] S. Mathew, K.S. Tustison, T. Sugatani, L.R. Chaudhary, L. Rifas, and K.A. Hruska, The mechanism of phosphorus as a cardiovascular risk factor in CKD. J Am Soc Nephrol 19 (2008) 1092-105.
[57] K.M. Swart, P. Lips, I.A. Brouwer, R. Jorde, M.W. Heymans, G. Grimnes, M.R. Grubler, M. Gaksch, A. Tomaschitz, S. Pilz, G. Eiriksdottir, V. Gudnason, L. Wamberg, L. Rejnmark, C.T. Sempos, R.A. Durazo-Arvizu, K.G. Dowling, G. Hull, Z. Skrabakova, M. Kiely, K.D. Cashman, and N.M. van Schoor, Effects of vitamin D supplementation on markers for cardiovascular disease and type 2 diabetes: an individual participant data meta-analysis of randomized controlled trials. Am J Clin Nutr 107 (2018) 1043-1053.
[58] S. Thanapluetiwong, A. Chewcharat, K. Takkavatakarn, K. Praditpornsilpa, S. Eiam-Ong, and P. Susantitaphong, Vitamin D supplement on prevention of fall and fracture: A Meta-analysis of Randomized Controlled Trials. Medicine (Baltimore) 99 (2020) e21506.
[59] J. Dong, S.L. Wong, C.W. Lau, H.K. Lee, C.F. Ng, L. Zhang, X. Yao, Z.Y. Chen, P.M. Vanhoutte,

ISSN 2618-1584 Vol. 5, Issue 3: 29-38, DOI: 10.25236/FMSR.2023.050305

and Y. Huang, Calcitriol protects renovascular function in hypertension by down-regulating angiotensin II type 1 receptors and reducing oxidative stress. Eur Heart J 33 (2012) 2980-90.
[60] T. Sun, and X. Yu, FGF23 Actions in CKD-MBD and other Organs During CKD. Curr Med Chem 30 (2023) 841-856.
[61] F. Bellone, M. Cinquegrani, R. Nicotera, N. Carullo, A. Casarella, P. Presta, M. Andreucci, G. Squadrito, G. Mandraffino, M. Prunestì, C. Vocca, G. De Sarro, D. Bolignano, and G. Coppolino, Role of Vitamin K in Chronic Kidney Disease: A Focus on Bone and Cardiovascular Health. Int J Mol Sci 23 (2022).
[62] M. Fusaro, F. Tondolo, L. Gasperoni, G. Tripepi, M. Plebani, M. Zaninotto, T.L. Nickolas, M. Ketteler, A. Aghi, C. Politi, G. La Manna, M.L. Brandi, S. Ferrari, M. Gallieni, M.C. Mereu, and G. Cianciolo, The Role of Vitamin K in CKD-MBD. Curr Osteoporos Rep 20 (2022) 65-77.
[63] H. Wang, L. Li, N. Zhang, and Y. Ma, Vitamin K2 Improves Osteogenic Differentiation by Inhibiting STAT1 via the Bcl-6 and IL-6/JAK in C3H10 T1/2 Clone 8 Cells. Nutrients 14 (2022).
[64] E. Zaragatski, J. Grommes, L.J. Schurgers, S. Langer, L. Kennes, M. Tamm, T.A. Koeppel, J. Kranz, T. Hackhofer, K. Arakelyan, M.J. Jacobs, and M. Kokozidou, Vitamin K antagonism aggravates chronic kidney disease-induced neointimal hyperplasia and calcification in arterialized veins: role of vitamin K treatment? Kidney Int 89 (2016) 601-11.