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Research Progress on Mineral and Bone Metabolism Disorders in Chronic Kidney Disease

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Abstract: Abnormal mineral and bone metabolism (MBD) is one of the most common complications in patients with chronic kidney disease (CKD), and an important factor in the occurrence of cardiovascular events and increased mortality in CKD patients. Abnormal calcium, phosphorus, parathyroid hormone (PTH), vitamin D metabolism, bone turnover, and vascular calcification are its abnormal manifestations. This article aims to review the research progress of CKD-MBD in recent years, to provide a reference for the clinical treatment of CKD-MBD.

1. Introduction

Chronic kidney disease (CKD) is the change of renal structure and function caused by various reasons. With the further development of CKD, various complications also occur, among which mineral and bone metabolism disorder (MBD) is one of the most common complications in CKD patients. In the past decades, the mineral and bone metabolism disorder related to CKD has been called "renal osteodystrophy (ROD)", and the clinical symptoms of patients are bone pain, fracture, skin itching, etc.[1,2]. Until 2006, KDIGO reached a consensus and proposed a new synonym "CKD-MBD"[3]. Compared with ROD, CKD-MBD has a wider range, more contents, and more details. It is characterized by abnormal regulation of serum calcium and phosphorus levels, and a significant increase in parathyroid hormone (PTH) levels[4,5]. The abnormalities of the above indicators often lead to changes in bone metabolism (including bone transformation and bone salt deposition), and increase the risk of vascular calcification and soft tissue calcification[3]. CKD-MBD is a potential risk factor for disability, cardiovascular incidence rate, and mortality[6, 7], and an important reason for poor quality of life[8] and increased mortality[9]. Some studies have shown that[10] CKD-MBD has a great impact on most patients with CKD stages 4 and 5. In 2009, KDIGO guidelines released that CKD-MBD includes one or more of the following situations: (1) abnormal metabolism of calcium, phosphorus, parathyroid hormone (PTH) and vitamin D[11]; (2) Bone transformation, mineralization, volume, linear growth and strength abnormality; (3) Calcification of blood vessels or other soft tissues. At present, the global attention and research on

CKD-MBD is getting higher and higher. This article aims to review the research progress of CKD-MBD in recent years.

2. Abnormal Mineral Metabolism

When CKD progresses, with the decrease of glomerular filtration rate (GFR), the ability to excrete phosphorus gradually weakens, causing the continuous increase of serum phosphorus. When serum phosphorus exceeds the normal excretion range of the glomerulus, hyperphosphatemia appears. The increase of serum phosphorus can transform smooth muscle cells into osteoblasts, thus leading to vascular calcification [12]. At the same time, the increase of blood phosphorus can stimulate the synthesis and secretion of PTH and promote the secretion of fibroblast growth factor-23 (FGF-23). Both of them work together on renal tubules to reduce phosphorus reabsorption. Traditionally, the decrease of serum 1,25 - (OH) 2D3 concentration in CKD patients is considered related to the decrease of renal function, but now it is considered that the increase of FGF-23 affects the kidney 1 α- Inhibition of hydroxylase. FGF-23 increases at the early stage of CKD, which affects the reduction of renal phosphorus excretion, and causes the decrease of serum 1,25 - (OH) 2D3 concentration and the increase of PTH. When the renal function is seriously damaged, the kidney generating 1 α- Hydroxylase is significantly reduced, resulting in the formation of 1,25 - (OH) 2D3 activity is also reduced, and the gastrointestinal absorption of calcium is reduced, leading to the occurrence of hypocalcemia. Under the stimulation of hypocalcemia, it affects the synthesis and secretion of PTH, promoting the enhancement of osteoclast activity, thus leading to bone calcium entering the blood(Figure1). Persistent hyperphosphatemia and hypocalcemia continuously stimulate the parathyroid gland, which can aggravate the hyperplasia of the parathyroid gland, and then secondary hyperparathyroidism (SHPT) occurs. It is reported that the incidence rate of SHPT is getting higher and higher. For CKD5 patients, the incidence rate of SHPT is as high as 20% - 25%[13]. However, the evaluation of SHPT still depends on the level of PTH. Studies have shown that the decline of renal function is related to the impairment of phosphate excretion and the reduction of 25 hydroxyvitamin D converted into 1,25-dihydroxyvitamin D, which then leads to the increase of the secretion of FGF-23 and phospholipids produced by PTH and bone cells, and ultimately leads to the imbalance of the absorption of calcium and phosphate by the gastrointestinal tract, which leads to bone turnover, so that the tissue has an inhibitory effect on calcium, thus affecting mineral metabolism, bone integrity and vascular calcification[14].

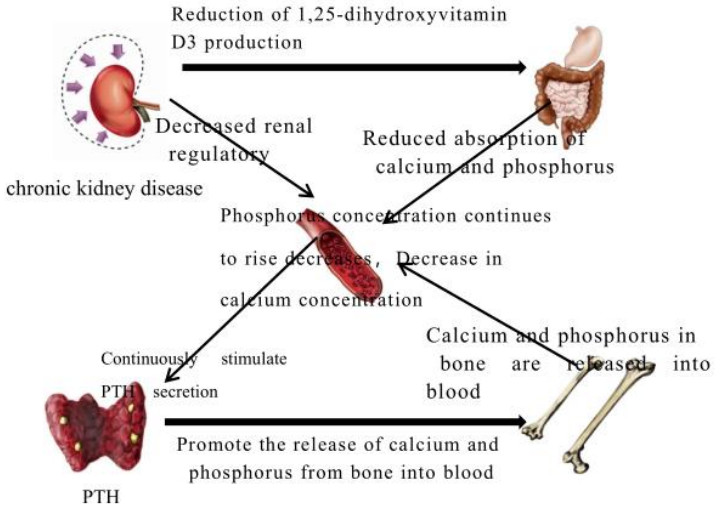

Figure 1: Mechanism of calcium and phosphorus metabolism imbalance.

3. Abnormal Bone Metabolism

The abnormal bone metabolism of CKD-MBD includes high transport osteopathy, low transport osteopathy, dynamic osteopathy, osteoporosis, etc. The appearance of SHPT enhanced the activity of PTH on osteoblasts and osteoclasts, leading to the appearance of high transport osteopathy. In the CKD period, not all patients will have high transport osteopathy. The main reason is that toxins accumulate in the body, causing osteoblasts and osteoclasts to have a resistance reaction to PTH, reducing bone formation in unit volume, lengthening the bone cycle, significantly slowing down the speed of bone formation and osteoclasts, and low transport osteopathy will also occur. However, high transport and low transport osteopathy can be converted under certain conditions. The main clinical manifestations are bone pain, fracture, bone deformity, and bone necrosis. PTH is related to normal bone turnover and the lowest mortality. The range of PTH is 150-300ng/L (about 15-30pmol/L)[12], and the risk of fracture is also related to the level of PTH[15]. Some studies have shown that[16], FGF-23 participates in and regulates bone mineral metabolism. Overexpression of FGF-23 signaling causes hypophosphatemia and low serum 1,25 (OH) 2D3 concentration, resulting in the occurrence of rickets[17].

4. Vascular Calcification

Vascular calcification is an abnormal deposition of calcium phosphate in blood vessels and tissues, and its pathological mechanism is complex. For CKD patients, vascular calcification is a common complication, accounting for 50% - 80% of patients in CKD stage 5[18]. In recent years, a large number of studies have found that vascular calcification is a process of transforming vascular smooth muscle into osteoblasts[19,20]. The calcification process is similar to bone formation[21], which will eventually lead to vascular calcification. When the minerals and bones in CKD patients are abnormal, it can promote the occurrence of vascular calcification[22]. The common vascular calcifications in CKD patients include intimal calcification, medial calcification, and valve calcification. The calcification of vascular intima, the decrease of vascular elasticity, and the increase of pressure can easily lead to the formation of atherosclerotic plaque and the occurrence of vascular rupture.

In the process of vascular calcification, there are a lot of inhibitors, such as pyrophosphate, adenosine, matrix Gla, protein, osteopontin, fetuin-A, etc. Under normal conditions, blood vessels and valves can keep the concentration of serum calcium and phosphate unaffected under the protection of these active inhibitors, and can prevent the abnormal deposition of minerals in soft tissues[20,23,24]. Hyperphosphaemia, hypercalcaemia, elevated PTH levels, oxidative stress, etc. are the inducing factors of CKD-MBD. Once the total volume of active inhibitors and inducers reaches equilibrium, calcification will occur in blood vessels and valves. Hyperphosphatemia, as an inducing factor of vascular calcification, is typical in CKD-MBD. In CKD patients, the increase of serum phosphorus is a key factor leading to vascular calcification, as well as a risk factor for cardiovascular mortality and incidence rate. At the same time, researchers have shown[25] that FGF-23 can reduce the calcification of human aortic smooth muscle cells, but this depends on α-Induction of Klotho.

5. FGF-23 and CKD-MBD

FGF-23 is a hormone secreted by osteoblasts and osteoblasts as a regulator of phosphate, vitamin D homeostasis, and bone mineralization. The increase of FGF-23 levels can affect the progress of renal disease in CKD patients, and is also closely related to the increase of cardiovascular risk, left ventricular hypertrophy, and mortality[26,27], which can lead to hypophosphatemia and bone

mineralization damage. It is reported that the increase of FGF-23 and the decrease of Klotho may be the earliest events of CKD-MBD. FGF-23 plays a role by binding with Klotho receptor to stimulate the activation of FGFR-1 and FGFR-3 receptors; PTH achieves this by combining with its specific receptors. They jointly reduce the concentration of sodium transporters NaPi2a and NaPi2c in a protein kinase A and protein kinase C dependent ways, thereby increasing the excretion of phosphate[28]. FGF-23 can also affect and reduce the expression of 1a hydroxylase, stimulate the expression of 24 hydroxylase, and reduce the overall level of active 1,25-dihydroxyvitamin D[29-31]. The main targets of FGF-23 are the parathyroid gland and kidney[32], and the specificity of FGF-23 targeting is defined by the receptor complex formed by FGF-23 receptor and Klotho[33].In conclusion, high phosphorus and high active vitamin D can promote the secretion of FGF23, and reduced blood phosphorus can reduce the production of bone FGF23(Figure2).

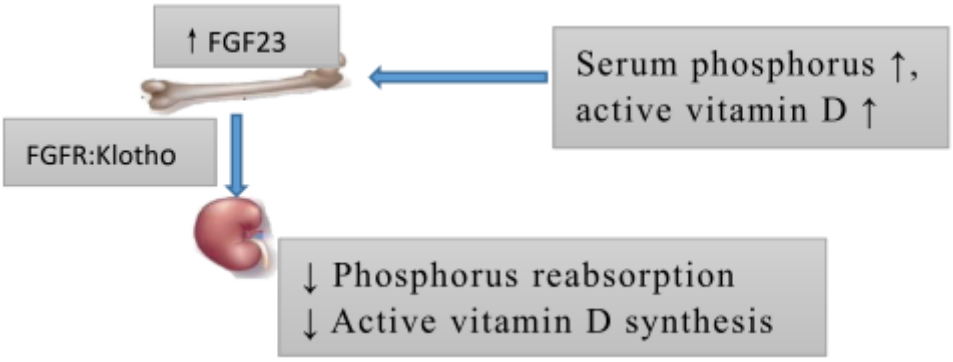

Figure 2: FGF-23 regulation.

6. Klotho and CKD-MBD

Klotho is a single transmembrane, anti-aging protein that protects the kidney and acts as a coreceptor for FGF-23. Klotho is mainly expressed in the tubular epithelium of the normal kidney. FGF-23 levels can be increased before changes in calcium, phosphorus, or PTH levels, and can be used as an early marker of the emergence of CKD-MBD[34,35]. However, due to the deficiency of Klotho, hyperphosphatemia is still the main regulator of FGF-23 secretion. The decrease of Klotho plays a crucial role in the pathogenesis of CKD, and there are potential mechanisms for anti-fibrosis, such as its inhibition of TGF-β, Wnt and FGF2 signaling pathways[36-38].It was reported[39] that klothor-derivedpeptide1 (KP1) protects the kidney by targeting TGF-β signal. KP1 binds to TGF-β receptor 2(TβR2) and destroys the binding of TGF-β/TβR2, thus inhibiting the activation of fibroblasts.To improve renal fibrosis. In severe CKD, Klotho expression was significantly downregulated[38,40].Klotho also prevents the development of kidney disease and reduces renal fibrosis. The expression of Klotho can cause the disorder of calcium and phosphorus metabolism, and inhibit ATP stimulation of actin cell skeletal remodeling and proteinuria[41].

7. Treatment of CKD-MBD

The ultimate goal of clinical treatment of CKD-MBD is to relieve patients' clinical symptoms, improve patients' quality of life, and reduce patients' clinical mortality. At present, symptomatic treatments are used for CKD-MBD, such as controlling blood calcium and phosphorus to maintain their normal levels; Control SHPT; Prevent the occurrence of vascular calcification.

7.1. Controlling Blood Phosphorus

7.1.1. Controlling Dietary Phosphorus Intake

The main source of phosphorus in the human body is diet. For patients with CKD, the blood phosphorus level can reflect the intake of phosphorus to some extent. Therefore, limiting phosphorus intake can control hyperphosphatemia. Some studies believe[42] that a reasonable low-phosphorus diet can effectively reduce the level of blood phosphorus, to reduce the harm of high phosphorus to the human body. KDIGO guidelines recommend no more than 800-1000mg of phosphorus per day in patients with CKD. In terms of diet, protein intake should be strictly restricted. High-protein diet is often rich in organophosphorus[43], which will lead to the increase of blood phosphorus in the body. A controlled study of hemodialysis patients[44] showed that a low protein diet and low phosphorus diet could significantly reduce blood phosphorus. In addition, a reasonable and effective phosphorus reduction diet plan should be formulated according to personal eating habits, and all kinds of foods rich in phosphorus, such as nuts, beans, dairy products and animal offal, etc. should be prohibited. For some low-phosphorus vegetables, it is recommended to blanch them with boiling water to ensure the normal level of blood phosphorus.

7.1.2. Phosphorus Binder

The commonly used phosphorus binders in clinic mainly include aluminum phosphorus binder, calcium phosphorus binders, and non calcium phosphorus binder. However, each has its advantages and disadvantages (Table 1).Aluminum containing phosphorus binder is formed by combining aluminum hydroxide and phosphate ions to form compounds to reduce serum phosphorus; And aluminum phosphate, as an insoluble substance, can be deposited in the intestinal tract and then discharged out of the body to reduce phosphorus. Studies have found that small doses of aluminum can cause poisoning, and it is rarely used at present. Calcium phosphorus binding agent has been considered as the most effective drug for reducing phosphorus in clinics. It can effectively bind phosphorus in the intestine. However, KDIGO guidelines recommend that the dosage of calcium phosphate adhesive should be limited in patients with hyperphosphatemia in CKD3-5 and with persistent or repeated hypercalcemia. Relevant studies have confirmed that[45], compared with non calcium phosphate binders, calcium phosphate binders are more likely to have hypercalcemia. As a calcium phosphorus binding agent, carvellam carbonate is a non-metallic preparation, which can not only effectively reduce the blood phosphorus level, but also report that compared with calcium phosphorus binding agent, the calcium phosphorus binding agent has the effect of preventing vascular calcification. A study by Gao Xiaofeng[46] shows that Seviram carbonate can not only maintain the normal level of blood phosphorus, but also improve the inflammatory state and reduce the nerve stimulation.

Table 1: Comparison of different types of phosphorus binders

Binder	advantage	shortcoming
Aluminous	Potent	Neurotoxicity, Osteopathy (Osteomalacia)
Calcic	Cheap and widely used	High calcium risk, less effective than aluminum preparation
Sevelamer	It can reduce vascular calcification caused by high calcium, reduce cholesterol and low density lipoprotein	Moderate effect, too high price

7.2. Control SHPT

The pathogenesis of SHPT is complex. Hyperphosphatemia, vitamin D deficiency, hypocalcemia, and elevated levels of FGF-23 are important factors that affect SHPT, and can lead to bone mineralization and bone turnover. Therefore, SHPT is often controlled clinically by controlling hyperphosphatemia and hypocalcemia, and controlling PTH within the target range according to KDIGO guidelines (Table 2).In recent years, calcitriol and vitamin D analogues (such as paricalciferol and alfacalciferol) have been considered as the main choice of SHPT treatment for CKD patients. However, one trial showed that[47], paricalciferol can increase the risk of hypercalcemia in CKD patients. Therefore, calcitriol or vitamin D analogues are only used for severe and progressive SHPT[47]. However, these drugs will have some harmful effects, so the use of severe and progressive SHPT, calcitriol, or vitamin D analogues should start from a low dose, but the occurrence of hypercalcemia should also be avoided. For patients with hypercalcemia, reduce or stop the use of calcitriol or other vitamin D. Finally, parathyroidectomy is still a good treatment for SHPT that is difficult to treat. For whether the blood phosphorus reaches the standard, corresponding measures should be taken and appropriate phosphorus lowering drugs should be selected according to the situation (Figure 3).

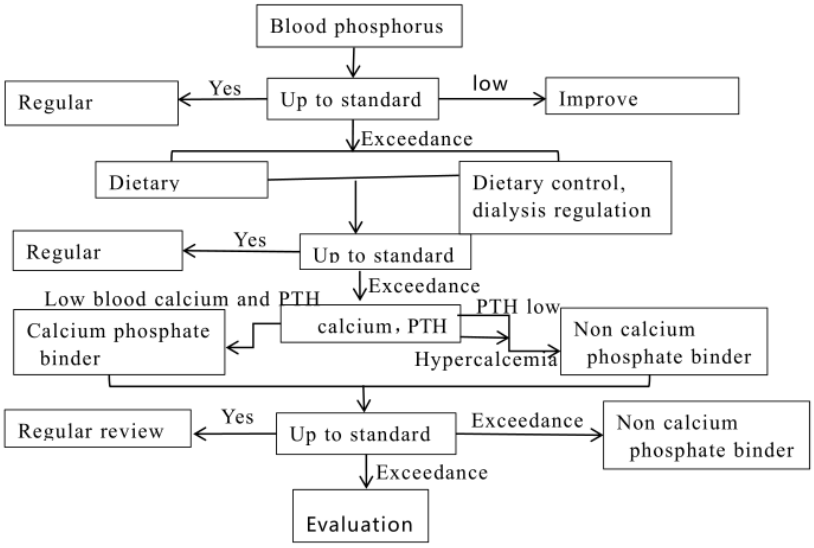

Figure 3: Blood phosphorus control process of CKD patients.

Table 2: Target value of PTH level

CKD stages	iPTH target value	Detection frequency
3(GFR30-59)	35-70 (viewpoint）	annually
4 (GFR15-29)	70-110（viewpoint）	Every 3 months
5 (<15Or dialysis）	150-300（evidence）	Every month

7.3. Prevention of Vascular Calcification

For many years, there is no definite treatment for vascular calcification. Increasingly evidence shows that the occurrence of vascular calcification in CKD patients can be effectively controlled by controlling phosphorus intake through diet, using binders to reduce blood phosphorus, hemodialysis and other methods. The use of calcium phosphate binders may better inhibit vascular calcification[48,49]. A study by Finch showed that[50], restriction of phosphorus can reverse

vascular calcification in rats with uremia. However, there are few studies on the inverse of vascular calcification by controlling blood phosphorus.

8. Summary

The incidence rate of CKD-MBD is getting higher and higher. The pathogenesis of CKD-MBD is more complex, and there are many pathogenic factors. Clinically, effectively control the level of calcium, phosphorus, and PTH to prevent vascular calcification and bone transformation. Pay attention to the influence of multiple factors in this disease, and find new methods to improve the quality of life of CKD-MBD patients and reduce the clinical mortality according to its characteristics. I hope that in the future, the medical community can explore new research methods and provide new ideas for the prevention and treatment of CKD-MBD.

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