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Research progress on the relationship between fibroblast growth factor 23 and chronic kidney disease

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Abstract

Chronic kidney disease(CKD)is now a global public health problem. In chronic kidney disease(CKD)patients，almost all have complications such as calcium and phosphorus metabolism disorders，hyperparathyroidism，cardiovascular disease，anemia，and inflammation，which seriously affect the progress and prognosis of CKD. Fibroblast growth factor 23(FGF23) is a bone-derived hormone that regulates the metabolism of phosphate and vitamin D. In the past，FGF23 was generally considered to play only an important role in the regulation of calcium and phosphorus metabolism. In recent years FGF23has been found to be associated with the occurrence or progression of various CKD complications. This opens up new horizons for studying the role of FGF23 in the course of chronic kidney disease. FGF23 is expected to become a new therapeutic target in the future，improving the prognosis of patients with CKD. This article will review the biological characteristics of FGF23 and its role in the progression of CKD. And briefly discuss its potential future role in chronic kidney disease.

Keywords: fibroblast growth factors; renal insufficiency; nephrology; phosphorus metabolism disorders; cardiovascular diseases

1.Introduction

Chronic kidney disease (CKD) is becoming an

increasingly prominent health problem, and its prevalence rate in China is 10.5% 8%[1]. As common complications of CKD patients, mineral metabolism disorders, cardiovascular events and endocrine system disorders not only seriously affect the long-term prognosis of CKD patients, but also significantly improve the mortality of CKD patients. Fibroblast growth factor 23 (FGF23) is a bone derived hormone that regulates the metabolism of phosphate and vitamin D. the concentration of FGF23 gradually increases with the decrease of glomerular filtration rate (GFR). Compared with healthy individuals, the concentration of FGF23 in patients with end-stage renal disease (ESRD) can be 1000 times higher[2]. At present, it is considered that the increase of FGF23 is an independent risk factor for the progression to end-stage renal disease and death in patients with CKD, which is closely related to the development and prognosis of chronic kidney disease. This article will review the biological characteristics of FGF23 and its role in the progression of CKD, and briefly discuss its potential role in chronic kidney disease.

2. Biological characteristics of FGF23

Molecular structure of FGF23 FGF23 was successfully identified in humans as early as 2000. FGF23 is a member of the fibroblast growth factor (FGFs) family. FGFs are composed of a core region containing 120 highly conserved amino acid residues and variable N-terminal and C-terminal residues[3]. The family contains at least 22 members[4], which is divided into 7 subfamilies, and FGF23 belongs to Fgf19 subfamily. FGF23 is synthesized and secreted by osteocytes and osteoblasts. In addition, FGF23 is also distributed in endothelial cells and pericytes of bone marrow venous sinus, thymus, lymph nodes and central paraventricular nucleus, but absent in the vascular bed of other organs[5,6]. Its gene is located on chromosome 12p13, which has 24% and 22% amino acid similarity with Fgf19 and FGF21 gene products. FGF23 is an endogenous protein composed of 251 amino acids with a molecular weight of about 32 KD. There are 24 amino acids in the N-terminal to form the signal peptide. The intermediate peptide chain is the homologous central region of FGF family, and 71 amino acids in the C-terminal are its unique sequence[7]. There is FGF receptor site at the amino terminal and Klotho protein binding site at the carboxyl terminal, which is the molecular structure basis for FGF23 to perform its function. FGF23 has two forms measured in human circulating blood: Full-length FGF23 (iFGF23) and inactive C-terminal FGF23 (cFGF23). CFGF23 is the product of iFGF23 cleavage. Only complete full-length FGF23 is considered to activate FGFR/α Klotho complex and downstream signaling pathway[8].

The role of FGF23 related receptor FGF23 is

mediated by FGF receptor (FGFR). FGFR can be divided into four types, namely FGFR1, FGFR2, FGFR3 and FGFR4. The different shear modes of fgfr1-3 extracellular D3 domain form specific B-segment and C-segment receptor isoforms[9]. FGF23 can bind to a variety of FGFRs, but it has low affinity and needs to be in cofactors α. With the help of Klotho protein, the signal transduction pathway can be activated. Liu s et al.[10] showed that FGF23 can bind to fgfr1c, fgfr3c and FGFR4 in vitro, but the exact receptor subtype activated by FGF23 in vivo is still unclear. In FGFR3 and FGFR4 deficient mice, receptor deletion did not affect the level of blood phosphorus or 1,25 $(OH)_2$-$VitD_3$. Meanwhile, Wu al et al.[11] used selective antibody activator of FGFR1 to activate FGFR1. The results showed that the activation of FGFR1 receptor was enough to induce FGF23 expression and cause hypophosphatemia in adult mice, suggesting that FGFR1 may be the main target receptor involved in the physiological activity of FGF23.

FGF23 and Klotho protein Klotho Gene were discovered in 1997. At that time, mice that accidentally silenced the gene suffered from premature aging syndrome[12]. The gene is mainly expressed in distal convoluted tubules, parathyroid glands and choroid plexus. Then two other paralogous genes, β Klotho[13] and γ Klotho[14] was also found. Since then, the coding products of Klotho Gene have been divided into α Klotho、 β Klotho、 γ Klotho 3 species. α Klotho is highly expressed in kidney, parathyroid gland, brain and other organs, but less expressed in other organs[12]. α Klotho is divided into three types: membrane binding type, soluble type and secretory type[15] α Klotho is an important basis of FGF23 signal transduction pathway. Membrane binding type α Klotho is composed of two repeats (KL1 and KL2), which are mainly expressed in the distal and proximal tubules, and a small amount of expression in the inner medullary collecting tube. The N-terminal and α Klotho's KL2 domain interacts with FGFR, and the C-terminal of FGF23 combines with the pocket junction[16] formed by KL1 and KL2 domains to form an active ternary receptor complex to regulate the reabsorption of phosphate, sodium and calcium, 1,25 $(OH)_2$-$VitD_3$ metabolism and the expression of angiotensin converting enzyme 2 in the kidney[17]. Membrane Klotho, as a co replication factor of FGF23 receptor, increases the specificity of FGF23 receptor, stabilizes FGF/FGFR binding, and enhances[18] the role of Klotho dependent FGF23. However, a few years ago, it was found that FGFR4, a receptor subtype located in the heart and large vessels, can regulate FGF23 activity without the action of Klotho protein[19].

3. FGF23 and mineral metabolism

In all vertebrates from fish to humans, FGF23/FGFR/α. An established function of Klotho

ternary complex is to coordinate bone mineral metabolism and renal phosphate treatment[20]. On the one hand, FGF23 can directly regulate the metabolism of calcium and phosphorus in vivo. On the other hand, FGF23, together with 1,25 $(OH)_2$-$VitD_3$ and parathyroid hormone (PTH), can form the bone kidney parathyroid endocrine axis and play an important role in the regulation of minerals in vivo.

The direct regulation of calcium and phosphorus metabolism by FGF23 and the trans cellular transport of phosphate depend on the promotion of sodium PHOSPHORUS SYNERGISTIC transporter (NaPi). NaPi-2a and NaPi-2c are mainly expressed in the apical membrane of epithelial cells in the proximal tubule of kidney, while NaPi-2b is mainly expressed in intestinal epithelial cells. In the proximal renal tubules, FGF23 is associated with FGFR- α Klotho complex directly activates extracellular signal regulated kinase ERK1/2 and serum/glucocorticoid regulated kinase sgk-1 signals. Subsequently, sgk-1 phosphorylates Na + / H + exchange regulatory cofactor (NHERF) - 1 and down regulates the membrane expression of the key sodium phosphate cotransporter NaPi-2a, resulting in increased urinary phosphorus excretion [21-24]. In the distal renal tubules, FGF23 signaling pathway directly activates WNK4 through (ERK) 1 / 2 and (SGK) - 1. After WNK4 activation, it increases the membrane epithelial calcium channel TRPV5 and a large number of sodium chloride transporter NCC, and increases the absorption of calcium and sodium in the distal nephron[25].

Indirect regulation of calcium and phosphorus metabolism by FGF23. 1,25 $(OH)_2$-$VitD_3$ can increase the expression of NaPi-2b in intestinal epithelial cells and promote phosphorus absorption. It can promote calcium and phosphorus absorption of intestinal epithelial cells through the classical gene pathway of binding with NVDR[26], and enhance the osteoclastic effect of PTH, so as to increase blood calcium and phosphorus. 1,25 $(OH)_2$-$VitD_3$ can also inhibit PTH gene transcription and parathyroid cell proliferation. PTH mainly acts on kidney and bone. On the one hand, PTH can improve lα- The activity of hydroxylase further promotes the synthesis of 1,25 $(OH)_2$-$VitD_3$. On the one hand, it can inhibit NaPi dependent phosphorus absorption and increase urinary phosphorus excretion in the proximal tubule, promote calcium reabsorption and reduce urinary calcium excretion in the distal tubule, and break bone in the bone to make bone calcium enter the blood. FGF23 can indirectly affect calcium and phosphorus metabolism by regulating 1,25 $(OH)_2$-$VitD_3$ and PTH. 2.2.1 FGF23 and 1,25 $(OH)_2$-$VitD_3$FGF23 can inhibit CYP27B1 and enhance cyp24a1 expression in renal proximal tubules[27], CYP27B1 and cyp24a1 encode 1, respectively α- Hydroxylase and 24 hydroxylase [the former is an important enzyme for the hydroxylation of vitamin D in the kidney, while the

latter is an important enzyme for the metabolism of 1,25 $(OH)_2D$], resulting in a further decrease in the level of 1,25 $(OH)_2$-$VitD_3$. 1,25 $(OH)_2$-$VitD_3$ can promote the production of FGF23. 1,25 $(OH)_2$VitD3 mediates the formation of dimer between VCR and retinol X receptor (RXR) through acting on vitamin D receptor (VCR) on cells. The dimer can bind to the upstream promoter of FGF23 gene and then promote the production of FGF23[27].

Both in vitro and in vivo tests of FGF23 and PTH showed that FGF23-FGFR1- α Klotho complex can act on parathyroid gland, reduce PTH mRNA and inhibit parathyroid cell proliferation to inhibit PTH synthesis and secretion, and FGF23 can also up regulate parathyroid cell 1 α- Hydroxylase expression increases local 1,25 $(OH)_2$-$VitD_3$ synthesis to inhibit PTH synthesis[28]. On the contrary, PTH can increase the transcription level of FGF23 mRNA through nuclear receptor associated protein 1 (Nurr1) to promote the synthesis of FGF23[29].

4. FGF23 and CKD related complications

FGF23 and calcium and phosphorus metabolism disorder many studies have shown that the blood FGF23 level begins to rise in the early stage of CKD (ckd1-ckd3 stage)[30], while the blood phosphorus, calcium and PTH are still within the normal range, which may be the adaptive compensatory response made by the body to maintain the systemic phosphorus balance[31,32]. However, with the progress of CKD, FGF23 can rise tens of times or even thousands of times. On the one hand, the decrease of glomerular filtration rate leads to the decrease of FGF23 excretion, and with the progress of CKD, the expression of Klotho and FGFR is weakened[33], which makes FGF23 unable to form FGF23/FGFR/aklotho ternary complex to play the role of reducing phosphorus, and further positive feedback promotes the abnormal increase of FGF23; On the other hand, the decrease of glomerular filtration rate weakens the ability of renal phosphorus excretion. The role of FGF23 and PTH in promoting renal phosphorus excretion is not enough to offset the decrease of phosphorus excretion caused by glomerular filtration rate. Increased blood phosphorus can stimulate the rise of PTH and FGF23. A large amount of elevated FGF23 further reduces 1,25 $(OH)_2$VitD3. This series of complex chain reactions caused the metabolic disorders of calcium, phosphorus, 1,25 $(OH)_2$-$VitD_3$ and $_{PTH}$ in patients with advanced CKD.

The increase of FGF23 in CKD patients is also closely related to hyperparathyroidism. Firstly, a large amount of elevated FGF23 causes the lack of 1,25 $(OH)_2$-$VitD_3$. Therefore, 1,25 $(OH)_2$-$VitD_3$ can not effectively inhibit PTH gene transcription and parathyroid cell proliferation; Secondly, the expression level of Klotho decreased with the decrease of GFR[33].

Krajisnikt et al.[34] found that the expression of Klotho and FGFR1 in parathyroid tissue of patients with advanced CKD decreased, indicating that the signal of Klotho/FGF23 axis was interrupted due to the decrease of Klotho and FGFR1 in parathyroid tissue in advanced CKD, which weakened the inhibitory effect of FGF23 on PTH synthesis and further increased PTH.

FGF23 and vascular disease for decades, the main cause of death in hemodialysis patients is cardiovascular disease, in which vascular calcification and endothelial injury are the key potential processes. Donate-correaj et al.[35] found that the gene expression level of FGF23 in calcified vessels was higher than that in vascular samples with non calcified lesions, and observed the expression of FGFR1 and FGFR3 in calcified plaques. Whether the increase of these levels directly promotes the development of calcification process or the defense against vascular lesions is still a controversial issue. According to the data of jimbor et al. [36], in the absence of Klotho deficiency, exposure to FGF23 can enhance phosphorus induced vascular calcification by promoting the transdifferentiation of osteoblasts in the aortic ring of uremic rats. What is puzzling is that scialla et al.[37] found that FGF23 had no effect on phosphorus uptake or phosphorus Induced Calcification of VSMCs regardless of the phosphate concentration in the medium and whether exogenous soluble Klotho was added. Meanwhile, zhud et al. [38] reported that FGF23 can protect the blood vessels of mouse VSMCs through extracellular signal regulated kinase pathway. Obviously, more studies are needed to clarify the exact role of FGF23 in the pathogenesis of vascular calcification in CKD. Verkaikm et al.[39] found that FGF23 blockade can prevent CKD induced endothelial dysfunction, and FGF23 induced endothelial dysfunction may be related to the increase of asymmetric dimethylarginine (ADMA) level caused by high FGF23 concentration. Because ADMA can competitively inhibit endogenous nitric oxide synthase (NOS) to reduce the production of no and inhibit the proliferation of endothelial progenitor cells, resulting in vascular endothelial injury. ADMA is released by proteolysis and eliminated by renal excretion, but more is metabolized and degraded by dimethylargine dimethylaminohydrolase (DDAH), which is inhibited by reactive oxygen species (ROS). Recent studies have shown that FGF23 can induce endothelial cells to produce ROS[40]. Therefore, it is not excluded that FGF23 damages vascular endothelial cells by indirectly inhibiting the degradation of ADMA, but further research is needed to prove it.

FGF23 and uremic cardiomyopathy, uremic cardiomyopathy are very common in CKD patients. They are important factors for the increase of incidence rate and mortality of cardiovascular events in this population. Clinical studies in CKD patients show that

there is a significant correlation between serum FGF23 level and the prevalence of cardiovascular diseases, especially myocardial hypertrophy. FGF23 plays an important role in the pathophysiology of uremic cardiomyopathy. FGF23 has been proved to induce the hypertrophic growth of isolated neonatal rat ventricular cardiomyocytes without the involvement of cofactor Klotho and activate a large number of genes that can cause hypertrophy, including α-actinin、α-MHC、β-MHC, ANP and brain natriuretic peptide (BNP), and these effects seem to be mediated by calcineurin/NFAT pathway[41,42]. Grabnera et al.[43] found that FGFR4 knockout can prevent the development of left ventricular hypertrophy (LVH) and fibrosis in mice fed with high phosphorus diet (inducing the up regulation of FGF23), while the application of specific anti FGFR4 antibody in rats undergoing 5/6 partial nephrectomy can reduce the development of cardiomyopathy. It can be seen that FGF23 seems to rely on the activation of FGFR4 to mediate the calcineurin/NFAT signal cascade, resulting in myocardial hypertrophy and fibrosis. At the same time, BÖ ckmanni et al.[44] observed that FGF23 stimulates the expression of RAAS gene and induces NGAL mediated activation of mineralocorticoid receptor in ventricular myocytes and fibroblasts of 5/6 partial nephrectomy rats, suggesting that FGF23 may also mediate the activation of cardiac local RAAS and promote myocardial hypertrophy and fibrosis. However, its potential molecular mechanism is not clear and needs more research and exploration.

FGF23 and valve calcification cardiac valve calcification is one of the important risk factors of cardiovascular events in patients with CKD. Cardiac valve calcification can not only cause valve stenosis or insufficiency, but also lead to arrhythmia, myocardial ischemia and even sudden cardiac death. Manna et al.[45] found that the incidence of cardiac valve ectopic calcification in patients with elevated serum FGF23 was about three times higher than that in other patients by analyzing the relationship between FGF23 and cardiovascular complications in maintenance hemodialysis patients; Fu Yuling et al.[46] studied the relationship between FGF23 and soluble Klotho levels and cardiac valve calcification in patients with continuous ambulatory peritoneal dialysis, found that high-level FGF23 and low-level soluble Klotho are independent risk factors for cardiac valve artery calcification, and pointed out that FGF23 and soluble Klotho may become biological targets for the prevention and treatment of cardiac valve calcification in the future. However, the mechanism of heart valve calcification induced by FGF23 in patients with kidney disease is not clear, which may be indirectly caused by affecting calcium and phosphorus metabolism, which needs to be further studied in the future.

Anemia in FGF23 and renal anemia CKD is the

result of multiple factors such as erythropoiesis disorder, iron deficiency and inflammation. FGF23 plays a pleiotropic role in anemia. Some studies[47,48] found that the high circulating FGF23 level in patients with CKD can reduce the secretion of renal erythropoietin (EPO). The expression of serum epomrna increased in normal mice and 5/6 partial nephrectomy mice treated with FGF23 signal transduction blocking. However, the intracellular signal pathway required for this effect of FGF23 is unclear; In addition, it was also found that in the 5/6 nephrectomy mouse model, a single intraperitoneal injection of FGF23 blocking peptide increased the proportion of erythroid cells in the G2/M phase of the erythrocyte cycle, accompanied by a decrease in the frequency of erythrocyte apoptosis. Iron is the main raw material for hemoglobin synthesis, and iron deficiency is also common in patients with CKD, which is mainly due to the presence of inflammation[49], proinflammatory cytokines (such as IL-6, IL-1B, TNF)- α) Elevated levels will lead to the up regulation of ferritin, which in turn will inhibit the absorption of iron in the intestine, leading to anemia. Inhibiting FGF23 signal transduction with FGF23 blocking peptide can significantly reduce the expression of these inflammatory markers and ferritin[48]. In general, FGF23 can lead to renal anemia in the following ways: (1) reduce the secretion of EPO in the kidney; (2) It directly reduces the proportion of red blood cells in G2 / M phase of its cell cycle and enhances the apoptosis of red blood cells; (3) It enhances the inflammatory environment, which in turn promotes the excess of iron calmodulin and leads to the restriction of iron produced by erythrocytes.

FGF23 and inflammation in patients with CKD, FGF23 levels have been found to be associated with markers of inflammation and oxidative stress (e.g., IL-6, CRP, TNF)- α) And advanced oxidation of protein products[50]. Singh et al.[51] revealed through in vitro experiments and various animal models of excessive FGF23 that FGF23 can directly target the liver to enhance the inflammatory environment. Liver cells have high levels of FGFR4 expression in mammals, and α Klotho expression is deficient. Stimulated by high serum FGF23 levels, FGF23 binds to FGFR4 on the surface of hepatocytes to activate PLC γ/ After modulating the synthesis and secretion of nfcrp-4, the content of these signal markers of inflammation can be improved. In addition, FGF23 can also be independent of the frs2a/Ras/Raf/MEK/ERK signal path α Klotho affects macrophages and stimulates tumor necrosis factor α (TNF- α) Because macrophages highly express FGFR1, this effect may be mediated by FGFR1. In addition to these studies, Kato s et al.[53] proposed that many pro-inflammatory genes are regulated by FGF23, because FGF23 induced cytokine production is mainly due to NFAT activation, and NFAT can induce various

cytokine genes (such as TNF)- α， IL-2, IL-4 and IL-6). On the contrary, various acute and chronic inflammation can also directly promote the production of FGF23. Studies have shown that intraperitoneal injection of heat inactivated Brucella or IL-1 in wild-type mice can increase the level of FGF23 mRNA in bone and the level of serum C-terminal FGF23 protein by 10 times[54]; Similarly, IL-6 has been proved to be a novel regulator of FGF23[55]. In the state of acute and chronic inflammation, IL-6 induces the phosphorylation of signal transducer and activator of transcription 3 (STAT3) through soluble IL-6 receptor (sIL-6R) - mediated trans signaling, thereby enhancing the synthesis and secretion of FGF23 from bone; Glosse et al.[56] found that high concentrations of TNF- α It can increase the production of FGF23 in UMR106 cells in a dose-dependent manner. Therefore, it can be speculated that FGF23 and inflammatory cytokines induce the expression of each other, thus forming a vicious circle and aggravating the lesions of multiple tissues and organs in patients with CKD. If so, targeted therapy for related cytokines may not only have anti-inflammatory effects, but also reduce the concentration of FGF23 in circulation, which will greatly benefit patients with CKD.

5. Conclusions

In conclusion, in patients with CKD, high levels of FGF23 are associated with calcium and phosphorus metabolism disorders, hyperparathyroidism, cardiovascular disease, anemia, inflammation and other complications. Although the exploration of these pathogenesis has just begun, these findings provide new and important insights into the pathophysiological mechanism of CKD, and may provide new treatment options for clinical intervention of CKD. However, further research is needed to clarify the mechanism of the pleiotropic effect of FGF23 and further determine whether FGF23 is a modifiable risk factor and a potential target of therapeutic intervention. This may help reduce the incidence rate and mortality of multiple complications in CKD patients, thereby optimizing CKD treatment.

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