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An overview of fibroblast growth factor 23 and its role in kidney function

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Abstract
Fibroblast growth factor 23 (FGF23) is a hormone that plays a critical role in regulating mineral homeostasis in the body. Specifically, FGF23 acts on the kidneys to decrease the reabsorption of phosphate from the blood and into the urine. This process helps to reduce serum phosphate levels and maintain balance alongside other hormones such as PTH. The primary responsibility of FGF23 is to regulate the balance of phosphate in the body. It does this by acting on the kidney cells to decrease the reabsorption of phosphate from the blood and into the urine. This process allows the body to excrete excess phosphate to maintain normal serum phosphate levels in the blood. In addition to regulating phosphate levels, FGF23 also plays a role in the metabolism of vitamin D. FGF23 can increase the metabolism of vitamin D to an inactive form, reducing the amount of active vitamin D in the body. This reduction in active vitamin D levels leads to decreased intestinal absorption of dietary calcium and phosphate. Abnormal levels of FGF23 in the body have been associated with several health concerns, particularly in patients with chronic kidney disease. High levels of FGF23 have been linked to the development of bone loss, vascular calcification, and cardiovascular disease. Conversely, low levels of FGF23 have been associated with an increased risk of mortality and cardiovascular disease in patients with kidney disease.

Keywords: Osteocytes, Fibroblast growth factor 23, Diabetic nephropathy, Vitamin D, Kidney, Phosphate, Parathyroid hormone, Chronic kidney disease, Cardiovascular disease

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Introduction

Fibroblast growth factor 23 (FGF23) is a hormone that regulates the levels of phosphate and vitamin D in the body (1). The kidney is the major organ that regulates serum phosphate levels. FGF23 is produced by bone cells called osteoblasts and osteocytes, and it acts on the kidney to decrease the reabsorption of phosphate and increase the metabolism of vitamin D (2,3).

It has been shown that excess levels of FGF23 in the body lead to various complications, including chronic kidney disease, cardiovascular disease, and even death. In patients with kidney disease, the levels of FGF23 are often increased, which has been associated with decreased survival rates. The increase in FGF23 levels is believed to result from the decreased ability of the kidney to excrete phosphate and maintain normal serum phosphate levels (4-7).

In addition, increased levels of FGF23 have been associated with pathological conditions such as bone loss, muscle weakness, and anemia. Although these effects are likely mediated through FGF23's regulation of phosphate and vitamin D metabolism, the specific mechanisms by which FGF23 affects these conditions are still not fully understood (6,8).

There is also emerging evidence that FGF23 may be involved in the pathogenesis of other kidney diseases, such as the development and progression of diabetic nephropathy and the formation of kidney stones (9).

Search strategy

For this review, we searched PubMed, Web of Science, EBSCO, Scopus, Google Scholar, Directory of Open Access Journals (DOAJ) and Embase using the following keywords: Fibroblast growth factor 23, diabetic nephropathy, vitamin D, phosphate, parathyroid hormone, end-stage renal disease, cardiovascular disease, bone cells, osteoblasts, bone health, phosphate metabolism, calcium metabolism, 1,25-dihydroxyvitamin d, bone disease, and

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Implication for health policy/practice/research/ medical education

Fibroblast growth factor 23 (FGF23) is a hormone that plays a key role in regulating the levels of phosphate and vitamin D in the body. FGF23 is primarily produced by cells in bones, specifically by osteocytes, end-stage renal disease, osteoblasts

chronic kidney disease.

Fibroblast growth factor 23 and bone function and structure

Osteocytes are the most abundant cells in bone tissue and are responsible for many functions related to the maintenance and repair of bone. Osteoblasts, on the other hand, are bone-forming cells that produce new bone tissue (10).

Osteocytes produce and secrete FGF23 in response to various stimuli, such as high levels of serum phosphate and vitamin D. These signals cause the osteocytes to initiate a complex signaling pathway that leads to the production and secretion of FGF23 (11). Once secreted, FGF23 acts on the kidney cells to decrease the reabsorption of phosphate from the blood and into the urine. In addition to regulating phosphate levels, FGF23 has also been shown to have autocrine and paracrine effects on the bone tissue itself (4). Specifically, FGF23 can act on osteocytes to regulate bone formation and resorption. High levels of FGF23 have been associated with reduced bone mineral density and increased bone fractures, while low levels of FGF23 have been linked to increased bone mass and reduced fracture risk. Similarly, increased levels of vitamin D can also stimulate FGF23 production by osteocytes (4,12). Vitamin D is a hormone that regulates calcium homeostasis in the body and can affect phosphate metabolism. High levels of vitamin D can cause FGF23 production in osteocytes, which can then act on the kidneys to reduce serum phosphate levels (3,13). Other stimuli that can activate osteocytes to produce and secrete FGF23 include parathyroid hormone (PTH), inflammatory cytokines, and bone matrix-derived factors (11,14).

In addition to high levels of serum phosphate and vitamin D, there are several other stimuli that can activate osteocytes to produce and secrete FGF23:

1. Parathyroid hormone is a hormone that regulates calcium metabolism in the body. When calcium levels in the blood are low, the parathyroid gland secretes PTH to stimulate calcium release from bone tissue. PTH also stimulates FGF23 secretion from osteocytes, which then acts on the kidneys to decrease the reabsorption of phosphate from the blood (15).
2. Bone matrix-derived factors: Osteocytes are embedded in the mineralized matrix of bone tissue, and they can sense changes in the surrounding environment. Certain stimuli that affect bone tissue, such as mechanical loading or damage, can activate osteocytes to produce and secrete FGF23 (10, 16).
3. Inflammatory cytokines: There is evidence to suggest that certain inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-alpha), interleukin-6 (IL-6), and interleukin-1 (IL-1), can stimulate FGF23 production by osteocytes. This has been observed in various autoimmune and inflammatory conditions (17,18).

Effects of parathyroid hormone on FGF23 secretion

Parathyroid hormone stimulates FGF23 secretion from osteocytes by activating specific signaling pathways within the cells. The precise mechanisms by which PTH regulates FGF23 production are not yet fully understood, but recent research has provided some insights into this process (2,4).

It is known that PTH can affect FGF23 production through several pathways. One way is by activating cyclic AMP (cAMP) signaling, which can stimulate FGF23 production in osteocytes. Specifically, when PTH binds to its receptor on osteocytes, it triggers the production of cAMP within the cell, which in turn stimulates FGF23 synthesis and secretion (19,20).

In addition to cAMP signaling, PTH may also regulate FGF23 production by activating the Wnt signaling pathway. The Wnt pathway is involved in bone formation and remodeling, and it has been shown that PTH can activate this pathway in osteocytes, leading to increased FGF23 production (21,22).

Effects of parathyroid hormone on osteocytes

Parathyroid hormone activates several signaling pathways in osteocytes to stimulate FGF23 production (4). The precise mechanisms by which PTH regulates FGF23 production are not yet fully understood, but recent research has provided some insight into this process.

One signaling pathway that PTH activates in osteocytes is the cAMP signaling pathway. Specifically, when PTH binds to its receptor on the osteocyte membrane, it triggers the production of cAMP within the cell. This cAMP signaling cascade ultimately leads to the activation of several genes involved in FGF23 production and secretion (19,23).

Another signaling pathway that PTH activates in osteocytes is the Wnt signaling pathway. The Wnt pathway plays a role in bone formation and remodeling, and it has been shown that PTH can activate this pathway in osteocytes. This activation can lead to the production of Wnt ligands, which can subsequently stimulate FGF23 synthesis and secretion (24).

Finally, PTH can also activate various other intracellular signaling pathways, such as the protein kinase A (PKA) and protein kinase C signaling pathways. These pathways can impact FGF23 production through their effects on gene expression and protein synthesis (23,25).

The cAMP signaling pathway plays an important role in regulating FGF23 production by osteocytes. When PTH or other stimuli activate the cAMP signaling pathway, it triggers a series of events that ultimately lead to increased FGF23 synthesis and secretion (26, 27).

The cAMP signaling pathway is initiated when PTH or other stimuli bind to their receptors on the osteocyte membrane. This binding triggers the activation of a G protein, which then activates adenylate cyclase. Adenylate cyclase converts ATP to cAMP, which then activates PKA (23,8). PKA subsequently activates several transcription factors involved in FGF23 gene expression, such as CCAAT/enhancer-binding protein (C/EBP) beta and early growth response protein (EGR). These factors can promote synthesis and secretion of FGF23 by the osteocyte (29,30).

Moreover, cAMP signaling has been shown to inhibit the degradation of FGF23, resulting in higher levels of circulating FGF23. This effect has been observed in various animal and human studies (9).

FGF23 gene expression in osteocytes

There are several transcription factors involved in FGF23 gene expression in osteocytes. These factors are activated in response to various stimuli, such as high levels of serum phosphate, vitamin D, and PTH (2,4).

Some of the transcription factors involved in FGF23 gene expression in osteocytes includes:

1. Early growth response protein 1 (EGR-1): EGR-1 is a zinc finger transcription factor that has been shown to activate FGF23 transcription in response to stimuli such as high levels of phosphate (31).
2. CCAAT/enhancer-binding protein beta (C/EBP-β): C/EBP-β is a transcription factor that can bind to the FGF23 promoter and activate its transcription in response to PTH and other stimuli (32).
3. Phosphate-regulating gene with homologies to endopeptidases on the X chromosome (PHEX): PHEX may play a role in FGF23 gene expression and regulation by binding to and cleaving a protein called DMP-1 (dentin matrix protein 1). DMP-1 can inhibit FGF23 transcription, so PHEX cleavage may remove this inhibitory effect (33,34).
4. Activator protein-1 (AP-1): AP-1 is a transcription factor complex that includes various members such as c-Fos and c-Jun. AP-1 can bind to the FGF23 promoter and activate its transcription in response to PTH and other stimuli (35,36).
5. Nuclear factor of activated T cells (NFAT): NFAT is a transcription factor that can regulate FGF23 expression in response to a signal from the calcium-sensing receptor in osteocytes (37).

FGF23 and phosphate homeostasis

Dysregulation of FGF23 expressions or function can lead to various health disorders related to mineral metabolism, mineralization, and bone health. FGF23 has an essential role in maintaining phosphate homeostasis in the body (38).

Hypophosphatemic rickets

This is a genetic disorder that causes low levels of phosphate in the blood and leads to inadequate mineralization of bones. The most common form of this disease is caused by mutations in the PHEX gene, which results in elevated levels of FGF23 in the blood. These high levels of FGF23 cause phosphate wasting in the kidneys and impair the normal functioning of vitamin D, leading to impaired bone modeling and mineralization (39,40).

Tumor-induced osteomalacia

Certain types of tumors, such as osteoblastomas and hemangiopericytomas, produce high levels of FGF23, which can cause phosphate wasting in the kidneys, leading to low levels of phosphate in the blood. This condition leads to osteomalacia, which is a softening of the bones that can result in fractures (41,42).

Autosomal dominant hypophosphatemic rickets

This is another form of genetic rickets caused by mutations in the FGF23 gene. These mutations lead to elevated levels of FGF23 in the blood, causing phosphate wasting in the kidneys. Low levels of phosphate in the blood can lead to soft and weak bones, and several other symptoms like dental abnormalities, short stature among others (43,44).

Hyperphosphatemia

FGF23 dysregulation can also lead to hyperphosphatemia, which is an elevated level of phosphate in the blood. This can occur when FGF23 signaling is impaired due to mutations or other causes, leading to decreased FGF23 activity. This condition can cause calcium-phosphate deposition in soft tissues, cardiovascular disease, and various other health complications (45,46).

Secondary hyperparathyroidism

FGF23 dysregulation can lead to secondary hyperparathyroidism resulting in elevated levels of PTH in response to low levels of serum calcium. High levels of PTH can cause increased bone resorption and depleted calcium levels in the bones, leading to further health concerns (47).

Fibroblast growth factor 23 and kidney function and structure

In the kidney, FGF23 decreases the expression of sodium-phosphate cotransporters (NaPi-2a and NaPi-2c) on the membrane surface of renal cells. This effect reduces the amount of phosphate that is reabsorbed from the urine back into the bloodstream, leading to increased urinary excretion of phosphate (46,48).

Moreover, FGF23 can also reduce the production

of 1,25-dihydroxyvitamin D (calcitriol), the active form of vitamin D. Calcitriol increases intestinal phosphate absorption by increasing the expression of NaPi transporters in the small intestine and increasing renal phosphate reabsorption. By decreasing calcitriol production, FGF23 can attenuate both of these actions and reduce phosphate levels in the blood (2,49).

FGF23 acts on the proximal renal tubules of the kidney, where it binds to FGF receptor 1 (FGFR1) in the presence of the co-receptor klotho. This binding leads to the inhibition of sodium-phosphate cotransporters (NaPi-2a and NaPi-2c) on the luminal membrane of the renal cells. These transporters mediate the reabsorption of phosphate from the urine back into the bloodstream. By reducing their activity, FGF23 limits phosphate reabsorption and increases the excretion of phosphate in urine, thus reducing serum phosphate levels (50).

FGF23 also inhibits the production of 1,25-dihydroxyvitamin D (calcitriol), which is a hormone that increases phosphate absorption from the small intestine and renal phosphate reabsorption. Calcitriol acts on intestinal cells and renal cells to increase the expression of NaPi transporters, leading to increased phosphate reabsorption. By inhibiting calcitriol production, FGF23 reduces the overall effect of NaPi transporters on serum phosphate levels (2,51).

FGF23 signaling and hyperphosphatemia

Dysregulation of FGF23 expression or function can have significant implications for mineral metabolism and related health conditions. Dysregulation of FGF23 signaling can lead to hyperphosphatemia (elevated levels of phosphate in the blood) and, consequently, secondary hyperparathyroidism through different mechanisms (52).

High levels of FGF23, such as those observed in hypophosphatemic rickets and Tumor-induced osteomalacia, increase renal phosphate excretion, leading to hypophosphatemia (low levels of phosphate in the blood). Conversely, low levels of FGF23, as in autosomal dominant hypophosphatemic rickets and some genetic disorders like autosomal dominant hypophosphatemic rickets (ADHR), impair renal phosphate excretion, leading to hyperphosphatemia (2,53).

Hyperphosphatemia leads to the deposition of calcium-phosphate crystals in soft tissues throughout the body including the kidneys, blood vessels, and heart, leading to tissue damage and various health complications such as cardiovascular diseases (54).

Moreover, hyperphosphatemia also suppresses the production of calcitriol (1,25 dihydroxycholecalciferol), the active form of vitamin D, in the kidneys, leading to hypocalcemia (low levels of calcium in the blood). Low levels of calcium stimulate the secretion of PTH, which acts on bone tissue to release calcium in the bloodstream, leading to secondary hyperparathyroidism (55).

Treatment typically involves phosphate-lowering agents such as phosphate binders and calcimimetics and requires close monitoring of calcium and phosphate levels (56).

Specifically, FGF23 acts on the proximal renal tubules of the kidney, where it binds to FGFR1 in the presence of the co-receptor, klotho protein. This binding leads to the activation of intracellular signaling pathways, which ultimately decrease the expression of sodium-phosphate cotransporters (NaPi-2a and NaPi-2c) on the luminal membrane surface of the renal cells (2,4).

NaPi-2a and NaPi-2c are responsible for the reabsorption of phosphate from the renal tubules back into the bloodstream. By reducing their expression, FGF23 reduces the amount of phosphate that is reabsorbed and increases the amount of phosphate that is excreted in the urine. This process helps to maintain balance and prevent hyperphosphatemia (4,48).

In addition to regulating NaPi transporters, FGF23 can also reduce the expression of the 1-alpha hydroxylase enzyme, which is responsible for converting 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D (57,58). The latter is an active form of vitamin D that increases phosphate absorption from the small intestine and increases renal phosphate reabsorption. By decreasing calcitriol production, FGF23 can attenuate both of these actions and further reduce phosphate levels in the blood (3).

Clinical implications of hyperphosphatemia and secondary hyperparathyroidism

Hyperphosphatemia (elevated levels of phosphate in the blood) and secondary hyperparathyroidism (excess secretion of PTH) have significant implications for health and can lead to various complications (59).

Chronic kidney disease-mineral and bone disorder

Hyperphosphatemia and secondary hyperparathyroidism often occur in people with chronic kidney disease and end-stage renal disease (ESRD). The damage to the kidneys impairs their ability to regulate phosphate levels and leads to the accumulation of phosphate in the blood, along with decreased levels of calcium (60). Excess PTH secretion leads to bone resorption and weakening of the bones. Together, these abnormalities contribute to chronic kidney disease-mineral and bone disorder, a complex disorder that increases the risk of fractures, cardiovascular disease, and mortality in chronic kidney disease and ESRD patients (61,62).

Vascular calcification

High levels of phosphate in the blood can lead to the deposition of calcium-phosphate crystals in soft tissues such as blood vessels. Vascular calcification can impair blood flow, reduce vessel elasticity, and increase cardiovascular risk (63).

Osteoporosis and fractures

Secondary hyperparathyroidism can cause calcium depletion from the bones and lead to an increased risk of osteoporosis and fractures.

Metabolic syndrome

Hyperphosphatemia has been linked to an increased risk of insulin resistance, obesity, and other components of metabolic syndrome (63).

Worsening kidney disease

When untreated, hyperphosphatemia and secondary hyperparathyroidism can move beyond chronic kidney disease-mineral and bone disorder and worsen baseline kidney disease. Over time, the strain of responding to hyperphosphatemia may damage the kidneys further (64). Overall, hyperphosphatemia and secondary hyperparathyroidism have significant implications for health and require proper management to prevent complications.

Conclusion

In summary, FGF23 plays a crucial role in regulating phosphate and vitamin D metabolism and maintaining normal kidney function. However, elevated levels of FGF23 have been associated with several adverse effects, including chronic kidney disease, cardiovascular disease, bone loss, muscle weakness, and anemia. Further studies are needed to fully understand the mechanisms by which FGF23 affects these various conditions and to develop targeted treatments to manage FGF23-related complications in patients with kidney disease.

Authors' contribution

Conceptualization: NA and HM.
Validation: SD.
Investigation: AF.
Resources: MA.
Data curation: SA.
Writing–original draft: NA, SD, and HM.
Writing–review and editing: SA, MA, and AF.
Visualization: SD.
Supervision: SA.
Funding acquisition: All authors.

Conflicts of interest

The authors declare that they have no competing interests.

Ethical issues

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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