Diagnostic Modalities for FGF23-Producing Tumors in Patients with Tumor-Induced Osteomalacia

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Fibroblast growth factor 23 (FGF23) is a hormone that is produced by osteocytes and regulates phosphate and vitamin D metabolism through binding to the Klotho-FGF receptor complex. Excessive actions of FGF23 cause several kinds of hypophosphatemic rickets/osteomalacia. Tumor-induced rickets/osteomalacia (TIO) is a paraneoplastic syndrome caused by overproduction of FGF23 from the responsible tumors. Because TIO is cured by complete resection of the causative tumors, it is of great clinical importance to locate these tumors. Several imaging methods including skeletal survey by magnetic resonance imaging and octreotide scintigraphy have been used to identify the tumors that cause TIO. However, none of these imaging studies indicate that the detected tumors are actually producing FGF23. Recently, systemic venous sampling was conducted for locating FGF23-producing tumor in suspected patients with TIO and demonstrated that this test might be beneficial to a subset of patients. Further studies with more patients are necessary to establish the clinical utility of venous sampling in patients with TIO.

Keywords: Fibroblast growth factor 23; Hypophosphatemia; 1,25-Dihydroxyvitamin D; Sampling

INTRODUCTION

Rickets and osteomalacia are diseases characterized by impaired mineralization of bone matrix. While rickets and osteomalacia are caused by the same etiologies, rickets develops in children before the closure of growth plates. There are diverse causes of rickets and osteomalacia. However, chronic hypophosphatemia underlines most cases of rickets and osteomalacia. Fibroblast growth factor 23 (FGF23) was identified as a responsible gene for autosomal dominant hypophosphatemic rickets/osteomalacia (ADHR) by positional cloning [1]. Almost simultaneously, FGF23 was cloned as a causative humoral factor for tumor-induced rickets/osteomalacia (TIO), a paraneoplastic syndrome with hypophosphatemia [2]. Since then, it has been shown that FGF23 is produced mainly by osteocytes, binds to the Klotho-FGF receptor complex and works as a phosphotrophic hormone as a physiological regulator of serum phosphate level [3]. In this review, diseases caused by excessive actions of FGF23 are summarized with an emphasis on TIO.

ACTIONS OF FGF23

FGF23 is one of the FGF family members which are defined as humoral factors with a FGF homology region [4]. There are 22 FGF family members in humans and these FGF family members are divided into several subfamilies. FGF23 belongs to the FGF19 subfamily together with FGF19 and FGF21 [4]. After the cloning of FGF23, actions of FGF23 were examined using the recombinant FGF23 protein. Single injection of recombinant FGF23 in mice caused reduction in serum phos-
phate and 1,25-dihydroxyvitamin D \([1,25(\text{OH})_2\text{D}]\) levels [5]. Serum phosphate level is mainly determined by renal handling of phosphate. Most phosphate filtered from glomeruli is reabsorbed in proximal tubules by the actions of type 2a and 2c sodium-phosphate cotransporters (NaPi-2a, 2c). FGF23 reduces the expression of these cotransporters and inhibits phosphate reabsorption [5]. At the same time, FGF23 modifies the expression of vitamin D-metabolizing enzymes. The 1,25(\text{OH})_2\text{D} is produced from 25-hydroxyvitamin D \([25(\text{OH})\text{D}]\) by the action of 25(\text{OH})D-1α-hydroxylase. On the other hand, 25(\text{OH}) D-24-hydroxylase converts 25(\text{OH})D to 24,25-dihydroxyvitamin D \([24,25(\text{OH})_2\text{D}]\) and also 1,25(\text{OH})_2\text{D} to 1,24,25-trihydroxyvitami D \([1,24,25(\text{OH})_2\text{D}]\). Therefore, 25(\text{OH})D-1α-hydroxylase is an enzyme that increases serum 1,25(\text{OH})_2\text{D}, while 25(\text{OH})D-24-hydroxylase works to reduce serum 1,25(\text{OH})_2\text{D}. FGF23 reduces 1,25(\text{OH})_2\text{D} levels by suppressing the expression of 25(\text{OH})D-1α-hydroxylase and also enhancing 25(\text{OH})D-24-hydroxylase expression [5]. Because 1,25(\text{OH})_2\text{D} increases intestinal phosphate absorption, FGF23 decreases serum phosphate by suppressing both proximal tubular reabsorption and intestinal phosphate absorption. FGF23 is produced by bone [6] and works in the kidney, indicating that there should be a specific receptor for FGF23 in the kidney. While the affinity of FGF23 to canonical FGF receptors is low, it was shown that FGF23 can transduce signals through the Klotho-FGF receptor complex [7,8].

**FGF23-RELATED HYPOPHOSPHATEMIC DISEASES**

Table 1 summarized the disease of FGF23-related hypophosphatemia. The actions of FGF23 mentioned above have been confirmed in humans by the demonstration that high FGF23 levels cause several hypophosphatemic rickets/osteomalacia. Hypophosphatemia is one of the stimulators of 25(\text{OH})D-1α-hydroxylase and usually enhances serum 1,25(\text{OH})_2\text{D} [9]. However, in these hypophosphatemic diseases caused by excessive actions of FGF23, serum 1,25(\text{OH})_2\text{D} remains low to low normal in the presence of frank hypophosphatemia with impaired proximal tubular phosphate reabsorption. Several kinds of hypophosphatemic rickets with different modes of inheritance were believed to be caused by enhanced expression of FGF23 in bone and high circulatory FGF23. In particular, X-linked hypophosphatemic rickets (XLHR) is caused by mutations in the phosphate-regulating gene with homologies to endopeptidases on the X chromosome (\textit{PHEX}) [10]. As mentioned above, \textit{FGF23} was identified as a responsible gene for ADHR [1]. Furthermore, autosomal recessive hypophosphatemic rickets 1 and 2 (ARHR1, 2) are caused by mutations in dentin matrix protein 1 (\textit{DMP1}) and dentin phosphophatase/phosphodiesterase 1 (\textit{ENPP1}), respectively [11-14]. Mutations in \textit{PHEX}, \textit{DMP1}, and \textit{ENPP1} in these diseases are considered to be inactivating mutations. However, it is not clear at the moment how inactivating mutations in these genes cause enhanced expression of FGF23.

A part of the FGF23 protein is proteolytically cleaved between \textsuperscript{179}Arg-\textsuperscript{X}-\textsuperscript{179}Arg sequence recognized by enzymes that recognize the \textsuperscript{179}Arg-\textsuperscript{X}-\textsuperscript{179}Arg sequence before or during the process of secretion [15]. Mutations in patients with ADHR replace either \textsuperscript{179}Arg or \textsuperscript{179}Arg with other amino acids and destroy the consensus \textsuperscript{176}Arg-\textsuperscript{X}-\textsuperscript{179}Arg sequence recognized by enzymes that process FGF23 [1]. Therefore, the mutant FGF23 protein was shown to be resistant to the processing, suggesting that this resistance to the processing caused high FGF23 levels [16,17]. However, it is not entirely clear how mutations in FGF23 cause hypophosphatemic rickets. Because FGF23 works as a phosphotrophic hormone, the production of FGF23 should be tightly regulated. This implies that even when the mutant FGF23 proteins produced by mutations in this gene are more stable than wild-type FGF23, this does not result in excessive actions of FGF23 if the regulatory mechanisms of FGF23 production remain intact. Actually, it has been shown that FGF23

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**Table 1. FGF23-Related Hypophosphatemic Diseases**

| Disease Description | Gene(s) |
|---------------------|---------|
| X-linked dominant hypophosphatemic rickets (XLHR) | \textit{PHEX} |
| Autosomal dominant hypophosphatemic rickets (ADHR) | \textit{FGF23} |
| Autosomal recessive hypophosphatemic rickets (ARHR1) | \textit{DMP1} |
| Autosomal recessive hypophosphatemic rickets (ARHR2) | \textit{ENPP1} |
| McCune-Albright syndrome/fibrous dysplasia | Hypophosphatemic disease with dental anomalies and ectopic calcification | \textit{FAM20C} |
| Linear sebaceous nevus syndrome | Tumor-induced rickets/osteomalacia (TIO) | Hypophosphatemic rickets/osteomalacia by saccharated ferric oxide or iron polymaltose | \textit{PHEX}, \textit{DMP1}, and \textit{ENPP1} |
levels in patients with ADHR change with time and are not always high [18]. In some patients with ADHR, hypophosphatemia disappears with normalization of circulatory FGF23. Therefore, the regulatory mechanisms of FGF23 production seem to be disrupted when patients with mutations in FGF23 show hypophosphatemia and high FGF23 levels. Increased FGF23 levels have been also reported in hypophosphatemic patients with McCune-Albright syndrome and linear sebaceous nevus syndrome [19,20]. Recently, it was shown that mutations in family with sequence similarity 20, member C (FAM20C) cause FGF23-related hypophosphatemic disease with dental anomalies and ectopic calcification [21].

In addition to these genetic disorders, FGF23 also causes hypophosphatemic rickets/osteomalacia in acquired diseases. Typical examples are TIO and hypophosphatemic osteomalacia by administration of intravenous iron. It has been shown that certain preparations of intravenous iron such as saccharated ferric oxide and iron polymaltose cause hypophosphatemic osteomalacia. Evaluation of these hypophosphatemic patients showed that FGF23 was high [22,23]. Because FGF23 levels in hypophosphatemic patients with vitamin D deficiency and Fanconi syndrome are rather low [24], these results suggest that intravenous iron caused hypophosphatemia by increasing FGF23 levels. In addition, single injection of iron polymaltose in patients with iron-deficiency anemia increased FGF23 and impaired tubular reabsorption of phosphate [25]. Therefore, these iron preparations seem to cause hypophosphatemia by high FGF23 levels. However, the administration of dextrin citrato-iron (III) complex caused neither high FGF23 nor hypophosphatemia [23]. Therefore, it is not clear how these iron preparations cause increased levels of FGF23.

TIO

TIO is a paraneoplastic syndrome usually caused by slow-growing mesenchymal tumors. Most tumors responsible for TIO are now pathologically classified as phosphaturic mesenchymal tumor, mixed connective tissue variant [26]. It is not uncommon for patients with TIO to complain of severe muscle weakness and bone pain that profoundly affect quality of life. However, this disease can be cured by complete removal of responsible tumors, indicating that some humoral factor causes this disease. As in other FGF23-related hypophosphatemic diseases, patients with TIO show hypophosphatemia with impaired proximal tubular phosphate reabsorption. In addition, serum 1,25(OH)₂D is low to low normal. Furthermore, FGF23 is elevated in most patients with TIO and rapidly decreases after successful removal of responsible tumors [27,28]. All these results indicate that FGF23 is the principal humoral factor causing TIO.

Several other factors obtained from tumors in patients with TIO have been reported to show activities that inhibit phosphate transport in kidney cells, cause hypophosphatemia in vivo or impair mineralization of bone. These include secreted frizzled-related protein 4, matrix extracellular phosphoglycoprotein and FGF7 [29-31]. However, none of these humoral factors have been shown to be elevated in patients with TIO. Therefore, it is unlikely that one of these humoral factors works as a principal agent for the development of TIO. Still, it is possible that these factors work together with FGF23 and contribute to at least some aspects of TIO or other FGF23-related hypophosphatemic diseases.

ISSUES IN THE DIAGNOSIS OF TIO

As mentioned above, TIO is a curable disease by complete resection of the responsible tumors. Therefore, it is of pivotal clinical importance to locate the causative tumors in patients with TIO. However, the responsible tumors for TIO are often small and exist within bone, making them difficult to find. Several systematic imaging studies including skeletal survey by magnetic resonance imaging (MRI), or [¹⁸F]fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT), have been used for the detection of the responsible tumors for TIO [32,33]. In addition, somatostatin receptor scintigraphy has been shown to be useful in at least some patients with TIO because mesenchymal tumors often express various types of somatostatin receptors [34-36]. However, TIO is not a common disease and there are no large scale studies examining the utility of these imaging studies in the detection of responsible tumors for TIO.

Functional tumors like aldosterone-producing adenomas and adrenocorticotropin hormone-producing pituitary adenomas can be localized by venous sampling. This method is based on the assumption that the responsible tumor is the major or only source of the hormone in the patient. For example, in a patient with primary aldosteronism by single adenoma, aldosterone production from the contralateral adrenal gland is suppressed, resulting in a greater difference in aldosterone levels between adrenal veins. In patients with TIO, FGF23 levels rapidly decrease after complete removal of responsible tumors [37]. In our experience, FGF23 decreased to lower
than the lower limit of the reference range in successfully operated patients and became undetectable in five out of six patients (Fig. 1). These results suggest that FGF23 production from normal bone is suppressed and the causative tumors are the main or only sources of FGF23 in patients with TIO, raising the possibility that venous sampling is useful for the detection of responsible tumors. Other studies have also examined whether or not it is possible to identify the responsible tumors using the fact that TIO is caused by secretion of FGF23 from these tumors. We previously demonstrated a patient with hypophosphatemic osteomalacia who had noticed a subcutaneous tumor in the right inguinal region [37]. We suspected that this tumor was the cause of his hypophosphatemic osteomalacia. However, the patient reported that the tumor had been present for many years before the onset of symptoms. Therefore, we wanted to prove that the tumor was actually producing FGF23 and causing TIO in this patient. We collected venous samples from all of the major veins through a catheter inserted from the right femoral vein and measured FGF23 levels. The results showed that there was some difference in FGF23 levels in the veins of this patient, and FGF23 levels were higher in the draining and adjacent vein to the tumor. These results suggested that systemic venous sampling is useful for the identification of tumors responsible for TIO.

Since then, we have prospectively conducted systemic venous sampling in patients with suspected TIO [38]. We collected up to 22 samples from all the major veins in each patient and measured FGF23 levels. If there was a difference in FGF23 levels, subsequent imaging studies such as CT and MRI were conducted aimed at the region with high FGF23 levels. Using this method, we were able to identify responsible tumors in eight out of ten patients with suspected TIO in this series. However, FGF23 levels were virtually the same throughout the body in two patients and we could not find the tumors in those two patients. Fig. 2 shows another example of the results of venous sampling. FGF23 was high in this patient’s left external iliac vein and a tumor was found in the left femoral head.

Results of systemic venous sampling in 14 patients were also reported by another group [39]. They divided patients into two groups, with or without suspicious sites by prior imaging studies including octreotide scintigraphy, FDG-PET/CT, MRI,
and CT. They concluded that sampling is useful for patients with suspicious sites in order to confirm that the detected tumors are responsible for TIO. However, they indicated that this sampling is not useful in the absence of suspicious lesions by imaging studies. They have conducted venous sampling after imaging studies and this approach is different from ours. However, they could not find any difference in FGF23 levels in four patients without suspicious lesions, similar to two patients in our series. Therefore, it is clear that systemic venous sampling is not a perfect way to localize the responsible tumors for TIO. While octreotide scintigraphy has been shown to be useful in some cases, the sensitivity and specificity of this scintigraphy is unknown, partly because of the rarity of TIO. In addition, this scintigraphy is not available in several countries, including Japan. Therefore, several methods should be used to identify the responsible tumors and we believe that venous sampling is useful for at least some patients with suspected TIO as shown in several case reports [40-43].

**CONCLUSIONS**

TIO has been a difficult disease for clinicians. There was no specific biochemical marker for this disease before the identification of FGF23. The identification and the establishment of an assay method for FGF23 made the diagnosis and follow-up of patients with TIO easier. Still, while the definitive diagnosis of TIO depends on finding the causative tumors, there are no standard or perfect ways of finding them. Even if the responsible tumors are found, it is possible that these tumors cannot be completely removed because of the location of the tumors or the condition of the patients. While medical treatment with neutral phosphate and active vitamin D improves the symptoms of affected patients to some degree, these medications can be associated with adverse events such as diarrhea and secondary-tertiary hyperparathyroidism. In this respect, it is interesting to see whether the inhibition of FGF23 activity is useful for patients with hypophosphatemic rickets/osteomalacia caused by excessive activity of FGF23 (Table 1). Several methods such as anti-FGF23 antibodies, the C-terminal fragment of FGF23 that compete with intact FGF23 for the binding to the Klotho-FGF receptor complex, an inhibitor of extracellular signal-regulated kinase, and inhibition of FGF receptor have been shown to antagonize the actions of FGF23 and increase phosphate level in animals [44-48]. However, there are no data on the utility of these methods in humans except for anti-FGF23 antibody [49]. Clearly, better diagnostic methods for the localization of causative tumors and treatments are needed for patients with TIO.

**CONFLICTS OF INTEREST**

No potential conflict of interest relevant to this article was reported.

**ACKNOWLEDGMENTS**

This work was partly supported by grants from the Ministries of Education, Culture, Sports, Science and Technology and Health, Labor and Welfare of Japan.

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