

Overview

Useful For

Diagnosing and monitoring tumor induced osteomalacia

Diagnosing X-linked hypophosphatemia or autosomal dominant hypophosphatemic rickets

Diagnosing familial tumoral calcinosis with hyperphosphatemia

Highlights

Fibroblast growth factor 23 (FGF23) is a major regulator of phosphate homeostasis.

FGF23 measurements are useful in the differential diagnosis of hypophosphatemic diseases.

Intact FGF23 is elevated in patients with tumor induced osteomalacia (TIO) or X-linked hypophosphatemia (XLH).

Method Name

Chemiluminescence Based Quantitative Sandwich Immunoassay.

NY State Available

Yes

Specimen

Specimen Type

Serum

Specimen Required

Collection Container/Tube:

Preferred: Serum gel

Acceptable: Red top

Submission Container/Tube: Plastic vial

Specimen Volume: 0.5 mL

Collection Instructions: Centrifuge and aliquot serum into plastic vial.

Forms

If not ordering electronically, complete, print, and send a [Renal Diagnostics Test Request](#) (T830) with the specimen.

Specimen Minimum Volume

0.25 mL

Reject Due To

Gross hemolysis	Reject
Gross lipemia	OK

Specimen Stability Information

Specimen Type	Temperature	Time	Special Container
Serum	Refrigerated (preferred)	14 days	
	Frozen	90 days	

Clinical and Interpretive

Clinical Information

Fibroblast growth factor 23 (FGF23) is a major regulator of phosphate (phosphorus) homeostasis. FGF23 is secreted primarily by bone, followed by thymus, heart, brain and, in low levels, by several other tissues. High serum phosphate (phosphorus) concentrations stimulate FGF23 expression and secretion through a yet poorly understood mechanism. Only intact FGF23 is considered bioactive. Intact FGF23 interacts with a specific receptor on renal tubular cells, decreasing expression of type IIa sodium/phosphate cotransporters, resulting in decreased phosphate reabsorption. In addition, gene transcription of 1-alpha-hydroxylase is downregulated, reducing bioactive 1,25-dihydroxy vitamin D, thereby further decreasing phosphate reabsorption. Eventually, falling serum phosphate concentrations lead to diminished FGF23 secretion, closing the feedback loop.

Measurement of FGF23 can assist in diagnosis and management of disorders of phosphate and bone metabolism in patients with either normal or impaired renal function. When FGF23 levels are pathologically elevated in individuals with normal renal function, hypophosphatemia, with or without osteomalacia, ensues. This can occur in rare, usually benign, mixed connective tissue tumors that contain characteristic complex vascular structures, osteoclast-like giant cells, cartilaginous elements, and dystrophic calcifications. These neoplasms secrete FGF23 ectopically and autonomously (tumor-induced osteomalacia; TIO). In less than one-fourth of cases, a different benign or malignant soft tissue tumor type or, extremely rarely, a carcinoma, may be the cause of paraneoplastic FGF23 secretion. In either scenario, complete removal of the tumor cures the TIO.

Hypophosphatemia and skeletal abnormalities are also observed in X-linked hypophosphatemia (XLH) and autosomal dominant hypophosphatemic rickets (ADHR). In XLH, variants in the *PHEX* (phosphate-regulating neutral endopeptidase) gene, which encodes a cell-surface-bound protein-cleavage enzyme, affect bioactive FGF23 secretion. Although the pathogenesis of XLH is not fully understood, animal studies indicate that loss of *PHEX* function results in enhanced secretion of FGF23.

In ADHR, *FGF23* variants render the protein resistant to proteolytic cleavage, thereby increasing FGF23 levels. However, not all *FGF23* variants increase renal phosphate secretions. Variants that impair FGF23 signaling, rather than increase its protease resistance, are associated with the syndrome of familial tumoral calcinosis (ectopic calcifications) with hyperphosphatemia.

In patients with renal failure, FGF23 contributes to renal osteodystrophy. The patient's kidneys can no longer excrete sufficient amounts of phosphate. This leads to marked increases in FGF23 secretion as a compensatory response, aggravating the 1,25-dihydroxy vitamin D deficiency of renal failure and the consequent secondary hyperparathyroidism.

In circulation, intact FGF-23 is cleaved to generate two biologically inactive fragments, a N-terminal fragment and a C-terminal fragment. FGF23 has a rapid clearance and short half-life which ranges between 46 and 58 min for intact and C-terminal fragments, respectively. Different types of FGF-23 immunoassays are available, those targeting the

intact form (iFGF23), and those detecting C-terminal fragments (cFGF23). Various studies have suggested that iFGF23 assays are more sensitive than cFGF23 for the detection of FGF23 concentrations in patients with TIO and patients with XLH. In addition, iFGF23 concentrations are not affected by iron deficiency which may lead to false positive results when using cFGF23 assays.

Reference Values

Pediatric (<18 yrs): < or =52 pg/mL

Adults(> or =18 yrs): < or = 59 pg/mL

Interpretation

Increased fibroblast growth factor 23 (FGF23) concentrations are present in individuals with renal phosphate-wasting diseases such as autosomal dominant hypophosphatemic rickets (ADHR), autosomal recessive hypophosphatemic rickets (ARHR), X-linked hypophosphatemia rickets (XLH) and tumor induced osteomalacia (TIO). Clinically, FGF23 measurement is useful in the differential diagnosis of these hypophosphatemic diseases since the patient presents with high FGF23 levels along with hypophosphatemia. In other causes of hypophosphatemia, such as vitamin D deficiency, FGF23 levels are low. In FGF23-producing tumors, a decrease in FGF23 concentrations following surgery is a reliable indication of complete tumor resection.

Intact FGF23 concentrations are elevated in patients with TIO or XLH. A study detected elevations of intact FGF23 in 19 of 22 TIO cases (86%).(1) In XLH, elevations of intact FGF23 were observed in 88% of patients (9 of 10 children and 13 of 15 adults).(2) While levels of intact FGF23 in XLH are usually elevated, FGF23 concentrations within the reference interval do not exclude the disease and should be interpreted in the setting of phosphate concentrations (ie, an FGF23 concentration in the upper level of the reference interval in the context of hypophosphatemia might be indicative of XLH). In ADHR, FGF23 concentrations are not consistently elevated, and the severity of renal phosphate-wasting may wax and wane; FGF23 concentrations are normal during quiescent periods when serum phosphate levels are normal, and they are elevated during active, hypophosphatemic phases of the disease.(3) FGF23 concentrations are influenced by factors such as phosphate intake and vitamin D therapy. Therefore, intact FGF23 levels are most informative in untreated patients.

Cautions

Fibroblast growth factor 23 (FGF23) concentrations must be interpreted in conjunction with serum phosphate (phosphorus) measurements, as FGF23 will be elevated in other conditions that cause hyperphosphatemia in vivo. These include: renal failure, severe catabolic states (eg, severe systemic illness, uncontrolled type I diabetes mellitus, and severe starvation) vitamin D toxicity, intravenous phosphate treatment and very high phosphate diets, advanced malignancy in particular with tumor lysis, crush or other significant muscle injury or destruction, fractures, and some endocrine disorders, in particular hypoparathyroidism and acromegaly. With the exception of renal failure, FGF23 measurements will not contribute to diagnosis or patient management in these situations.

Do not interpret FGF23 concentrations as absolute evidence of the presence or the absence of tumor induced osteomalacia (TIO). Some patients with TIO may have FGF23 levels within the reference interval. It is thought that tumors in these individuals may be secreting different, and yet unidentified, phosphatonins. Therefore, if the clinical picture and general osteomalacia laboratory workup suggest strongly that the patient has TIO; a normal intact FGF23 level should not discourage tumor search or removal.

Some patients who have been exposed to animal antigens, either in the environment or as part of treatment or imaging procedures, may have circulating anti-animal antibodies present. These antibodies may interfere with the assay reagents to produce unreliable results. Whenever the test results do not fit the clinical picture, the laboratory should be consulted regarding possible assay interference.

In vitro studies indicate that the presence of burosumab falsely decreases IFG23 results in a dose-dependent manner.

Patients receiving burosumab should not be monitored using the IFG23 assay. Serum phosphate, alkaline phosphatase, and 1,25(OH)₂D measurements should be considered for monitoring response to therapy.

Clinical Reference

1. Imel EA, Peacock M, Pitukcheewanont P, et al: Sensitivity of fibroblast growth factor 23 measurements in tumor-induced osteomalacia. *J Clin Endocrinol Metab.* 2006 Jun;91(6):2055-2061
2. Imel EA, Gray AK, Padgett LR, Econs MJ: Iron and fibroblast growth factor 23 in X-linked hypophosphatemia. *Bone.* 2014 Mar;60:87-92
3. Imel EA, Hui SL, Econs MJ: FGF23 concentrations vary with disease status in autosomal dominant hypophosphatemic rickets. *J Bone Miner Res.* 2007 Apr;22(4):520-526
4. Haffner D, Emma F, Eastwood DM, et al: Clinical practice recommendations for the diagnosis and management of X-linked hypophosphatemia. *Nat Rev Nephrol.* 2019 Jul;15(7):435-455. doi: 10.1038/s41581-019-0152-5
5. Fauconnier C, Roy T, Gillerot G, et al: FGF23: Clinical usefulness and analytical evolution. *Clin Biochem.* 2019 Apr;66:1-12. doi: 10.1016/j.clinbiochem.2019.03.002

Performance**Method Description**

The intact fibroblast growth factor 23 (FGF23) assay is a 2-site immunoenzymatic assay using two anti-human FGF23 mouse monoclonal antibodies. One antibody is coated onto microtiter wells and the other is alkaline phosphatase labeled. The signal generated is proportional to the concentration of intact FGF23 in the serum sample. The amount of intact FGF23 is determined by means of multipoint calibrator curve. Cross-reactivity of the assay with C-terminal FGF23 was evaluated in-house and determined to be no cross-reactivity with C-terminal FGF23 concentrations up to 230,680 pmol/L. (Package insert: MedFrontier FGF23 Intact. Hitachi Chemical Diagnostics Systems Co, Ltd; 08/2019)

PDF Report

No

Day(s) and Time(s) Test Performed

Wednesdays; 9 a.m.

Analytic Time

1 day

Maximum Laboratory Time

7 days

Specimen Retention Time

90 days

Performing Laboratory Location

Rochester

Fees and Codes

Fees

- Authorized users can sign in to [Test Prices](#) for detailed fee information.
- Clients without access to Test Prices can contact [Customer Service](#) 24 hours a day, seven days a week.
- Prospective clients should contact their Regional Manager. For assistance, contact [Customer Service](#).

Test Classification

This test was developed and its performance characteristics determined by Mayo Clinic in a manner consistent with CLIA requirements. This test has not been cleared or approved by the U.S. Food and Drug Administration.

CPT Code Information

83520

LOINC® Information

Test ID	Test Order Name	Order LOINC Value
IFG23	Intact Fibroblast Growth Factor 23	54390-0

Result ID	Test Result Name	Result LOINC Value
607216	Intact Fibroblast Growth Factor 23	54390-0