MAYO CLINIC LABORATORIES

Test Definition: IFG23

Intact Fibroblast Growth Factor 23, Serum

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 or X-linked hypophosphatemia.

Method Name

Chemiluminescence-Based Quantitative Sandwich Immunoassay

NY State Available

Yes

Specimen

Specimen Type

Serum

Specimen Required

Supplies: Sarstedt Aliquot Tube, 5 mL (T914)
Collection Container/Tube:
Preferred: Serum gel
Acceptable: Red top
Submission Container/Tube: Plastic vial
Specimen Volume: 0.5 mL Serum
Collection Instructions: Centrifuge and aliquot serum into a plastic vial.

Forms

If not ordering electronically, complete, print, and send 1 of the following forms with the specimen:
Renal Diagnostics Test Request (T830)
Oncology Test Request (T729)

Specimen Minimum Volume

Serum: 0.25 mL

Reject Due To

Gross hemolysis	Reject
Gross lipemia	Reject
Gross icterus	OK

Specimen Stability Information

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

Clinical & 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 kidney function. When FGF23 levels are pathologically elevated in individuals with normal kidney 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 kidney 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 hypophosphatemia that is not FGF23-mediated, such as renal Fanconi syndrome or primary defects of the renal sodium-dependent phosphate transporters, FGF23 is suppressed and concentrations are low or low-normal.(1) 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%).(2) In XLH, elevations of intact FGF23 were observed in 88% of patients (9 of 10 children and 13 of 15 adults).(3) While levels of intact FGF23 in XLH are usually elevated, intact FGF23 concentrations within the reference interval do not exclude the disease and should be interpreted in the setting of phosphate concentrations. In the setting of hypophosphatemia, an intact FGF23 concentration that is not suppressed, including a low-normal or upper-normal value, indicates inappropriate FGF23 activity and supports FGF23-mediated hypophosphatemia, of which XLH is the most common cause.(1) 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.(4) FGF23 concentrations are influenced by phosphate intake and vitamin D therapyTherefore, intact FGF23 levels are most informative before such therapy is started.(1)

In suspected XLH, intact FGF23 is recommended as part of the initial biochemical evaluation, together with serum phosphate, calcium, alkaline phosphatase, parathyroid hormone, 25-hydroxy and 1,25-dihydroxy vitamin D, creatinine, and urinary phosphate and calcium excretion (tubular maximum reabsorption of phosphate per glomerular filtration rate [TmP/GFR]). *PHEX* genetic testing is the preferred confirmatory test; when it is unavailable, a family history of X-linked inheritance with non-suppressed intact FGF23 in the presence of hypophosphatemia supports the diagnosis. If

PHEX analysis is negative, other FGF23-related disorders (*DMP1*, *ENPP1*, *FGF23*) and tumor-induced osteomalacia should be considered.(1)

In the setting of hypophosphatemia, an elevated FGF23 may be indicative of FGF23-mediated hypophosphatemia. In a Mayo Clinic study, using the Medfrontier (Minaris Medical Co, Ltd, Tokyo, Japan) and a cut-off of greater than or equal to 59 pg/mL, corresponding to the upper limit of the reference interval, intact FGF23 concentrations were elevated in 90% and 84% of TIO and XLH hypophosphatemia patients, respectively. In the TIO and XLH patients where the intact FGF23 concentration was not above the reference interval, the intact FGF23 concentrations were at the upper end of the reference interval and much higher than observed in the patients with FGF23-independent hypophosphatemia. In contrast in the patients with FGF23-independent hypophosphatemia, intact FGF23 concentrations were significantly lower than what was observed in the healthy cohort and the normophosphatemic patients.(5) A study using the same assay and a cut-off of 30.0 pg/mL, reported 100% sensitivity and 82% specificity for the differential diagnosis of FGF23-related hypophosphatemia rickets/osteomalacia without vitamin D deficiency versus non-FGF23-related hypophosphatemia.(6)

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 chronic kidney disease; 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 kidney failure, FGF23 measurements will not contribute to diagnosis or patient management in these situations.

Intravenous iron preparations, alcohol-induced FGF23 syndrome, and ectopic FGF23 production in advanced malignancy can also cause FGF23-mediated hypophosphatemia and should be considered when FGF23 is elevated.(1)

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 strongly suggest that the patient has TIO, a normal intact FGF23 level should not discourage tumor search or removal.

In rare cases, some individuals can develop antibodies to mouse or other animal antibodies (often referred to as human anti-mouse antibodies [HAMA] or heterophile antibodies), which may cause interference in some immunoassays. Caution should be used in interpretation of results, and the laboratory should be alerted if the result does not correlate with the clinical presentation.

Intact FGF23 should not be used to monitor patients receiving burosumab. Available FGF23 antibodies cannot distinguish free FGF23 from FGF23 bound to burosumab, which may produce falsely elevated results.(1,7) Response to burosumab therapy should be monitored with serum phosphate (ideally 7 to 14 days after injection), tubular maximum reabsorption of phosphate per glomerular filtration rate, alkaline phosphatase, and 1,25-dihydroxy vitamin D.(1)

Clinical Reference

1. Haffner D, Emma F, Seefried L, et al. Clinical practice recommendations for the diagnosis and management of X-linked hypophosphataemia. Nat Rev Nephrol. 2025;21(5):330-354

2. Imel EA, Peacock M, Pitukcheewanont P, et al. Sensitivity of fibroblast growth factor 23 measurements in tumor-induced osteomalacia. J Clin Endocrinol Metab. 2006;91(6):2055-2061
3. Imel EA, Gray AK, Padgett LR, Econs MJ. Iron and fibroblast growth factor 23 in X-linked hypophosphatemia. Bone. 2014;60:87-92
4. Imel EA, Hui SL, Econs MJ. FGF23 concentrations vary with disease status in autosomal dominant hypophosphatemic rickets. J Bone Miner Res. 2007;22(4):520-526
5. Ramos P, Larson B, Ashrafzadeh-Kian S, et al. Intact fibroblast growth factor 23 concentrations in hypophosphatemic disorders. Endocr Pract. 2023;29(3):193-198. doi:10.1016/j.eprac.2023.01.003
6. Ito N, Kubota T, Kitanaka S, et al. Clinical performance of a novel chemiluminescent enzyme immunoassay for FGF23. J Bone Miner Metab. 2021;39(6):1066-1075. doi:10.1007/s00774-021-01250-1
7. Ashrafzadeh-Kian SL, Ito N, Srivastava T, et al. The effect of burosumab on intact and C-terminal FGF23 measurements. Clin Endocrinol (Oxf). 2023;99(2):152-157. doi:10.1111/cen.14832
8. Fauconnier C, Roy T, Gillerot G, Roy C, Pouleur AC, Gruson D. FGF23: Clinical usefulness and analytical evolution. Clin Biochem. 2019;66:1-12. doi:10.1016/j.clinbiochem.2019.03.002
9. Hartley IR, Gafni RI, Roszko KL, et al. Determination of FGF23 levels for the diagnosis of FGF23-mediated hypophosphatemia. J Bone Miner Res. 2022;37(11):2174-2185. doi:10.1002/jbmr.4702

Performance

Method Description

The intact fibroblast growth factor 23 (FGF23) assay is a 2-site immunoenzymatic assay using 2 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.(Unpublished Mayo method)

PDF Report

No

Day(s) Performed

Tuesday, Thursday

Report Available

2 to 8 days

Specimen Retention Time

2 weeks

Performing Laboratory Location

Mayo Clinic Laboratories - Rochester Superior Drive

Fees & 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 account representative. 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. It has not been cleared or approved by the US 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