MAYO CLINIC LABORATORIES

Test Definition: IGFGP

Insulin-Like Growth Factor 1 and Insulin-Like Growth Factor-Binding Protein 3 Growth Panel, Serum

Overview

Useful For

Diagnosing growth disorders

Diagnosing adult growth hormone deficiency

Monitoring of recombinant human growth hormone treatment

Insulin-like growth factor binding protein 3 can be used as a possible adjunct to insulin-like growth factor 1 and growth hormone in the diagnosis and follow-up of acromegaly and gigantism

Profile Information

Test Id	Reporting Name	Available Separately	Always Performed
IGFMS	IGF-1, LC/MS, S	Yes	Yes
IGFB3	IGFBP-3, S	Yes	Yes

Method Name

IGFMS: Liquid Chromatography Mass Spectrometry (LC-MS)
IGFB3: Enzyme-Labeled Chemiluminescent Immunometric Assay

NY State Available

Yes

Specimen

Specimen Type

Serum

Necessary Information

Indicate patient's age and sex.

Specimen Required

Collection Container/Tube:
Preferred: Red top
Acceptable: Serum gel
Submission Container/Tube: 2 Plastic vials

Specimen Volume: 1 mL
Collection Instructions:
1. Centrifuge within 1 hour of collection.
2. Aliquot into 2 plastic vials in equal portions.

Specimen Minimum Volume
0.5 mL

Reject Due To

Gross hemolysis	Reject
Gross lipemia	OK

Specimen Stability Information

Specimen Type	Temperature	Time	Special Container
Serum	Frozen	14 days	

Clinical & Interpretive

Clinical Information
Insulin-like growth factor 1 (IGF1) is a 70-amino acid polypeptide (molecular weight [MW] 7.6 kDa). IGF1 is a member of a family of closely related growth factors with high homology to insulin that signal through a corresponding group of highly homologous tyrosine kinase receptors. IGF1 is produced by many tissues, with the liver being the main source of circulating IGF1. IGF1 is the major mediator of the anabolic and growth-promoting effects of growth hormone (GH). IGF1 is transported by IGF-binding proteins, in particular IGF-binding protein 3 (IGFBP3), which also controls its bioavailability and half-life.

IGFBP3 is a 264-amino acid peptide (MW 29 kD) produced by the liver. It is the most abundant of a group of IGFBPs that transport and control bioavailability and half-life of IGFs, particularly IGF1, the major mediator of the anabolic- and growth-promoting effects of GH. In addition to its IGF binding-function, IGFBP3 also exhibits intrinsic growth-regulating effects that are not yet fully understood but have evoked interest with regards to a possible role of IGFBP3 as a prognostic tumor marker.

Noncomplexed IGF1 and IGFBP3 have short half-lives (t1/2) of 10 minutes and 30 to 90 minutes, respectively, while the IGFBP3/IGF1 complex is cleared with a much slower t1/2 of 12 hours.

The secretion patterns of IGF1 and IGFBP3 mimic each other, their respective syntheses being controlled by GH. Unlike GH secretion, which is pulsatile and demonstrates significant diurnal variation, IGF1 and IGFBP3 levels show only minor fluctuations. IGF1 and IGFBP3 serum levels, therefore, represent a stable and integrated measurement of GH production and tissue effect.

Low IGF1 and IGFBP3 levels are observed in GH deficiency or GH resistance. If acquired in childhood, these conditions result in short stature.

Childhood GH deficiency can be an isolated abnormality or associated with deficiencies of other pituitary hormones. Some of the latter cases may be due to pituitary or hypothalamic tumors or result from either cranial radiation or intrathecal chemotherapy for childhood malignancies.

Most GH resistance in childhood is mild to moderate, with causes ranging from poor nutrition to severe systemic illness (eg, kidney failure). These individuals may have IGF1 and IGFBP3 levels within the reference range. Severe childhood GH resistance is rare and usually due to defects of the GH-receptor, its downstream signaling cascades, or deleterious variants in *IGF1*, its binding proteins, or its receptor signaling cascades.

Both GH deficiency and mild-to-moderate GH resistance can be treated with recombinant human GH (rhGH) injections, while severe resistance will usually not respond to GH. However, such patients might respond to recombinant IGF1 therapy, unless the underlying defect is in the IGF1 receptor or its downstream signaling systems.

The exact prevalence and causes of adult GH resistance are uncertain, but adult GH deficiency is seen mainly in patients with pituitary tumors. It is associated with decreased muscle bulk and increased cardiovascular morbidity and mortality, but replacement therapy remains controversial.

Elevated serum IGF1 and IGFBP3 levels often indicate either a sustained overproduction of GH or excessive rhGH therapy. Endogenous GH excess is caused mostly by GH-secreting pituitary adenomas, resulting in gigantism, if acquired before epiphyseal closure, and in acromegaly thereafter. Both conditions are associated with generalized organomegaly, hypertension, diabetes, cardiomyopathy, osteoarthritis, compression neuropathies, a mild increase in cancer risk (breast, colon, prostate, lung), and diminished longevity. It is plausible, but unproven, that long-term rhGH overtreatment may result in similar adverse outcomes.

Malnutrition results in low serum IGF1 concentrations, which recover with restoration of adequate nutrition.

Reference Values

INSULIN-LIKE GROWTH FACTOR 1
Males:
0-11 months: 18-156 ng/mL
1 year: 14-203 ng/mL
2 years: 16-222 ng/mL
3 years: 22-229 ng/mL
4 years: 30-236 ng/mL
5 years: 39-250 ng/mL
6 years: 47-275 ng/mL
7 years: 54-312 ng/mL
8 years: 61-356 ng/mL
9 years: 67-405 ng/mL

10 years: 73-456 ng/mL
11 years: 79-506 ng/mL
12 years: 84-551 ng/mL
13 years: 90-589 ng/mL
14 years: 95-618 ng/mL
15 years: 99-633 ng/mL
16 years: 104-633 ng/mL
17 years: 107-615 ng/mL
18-22 years: 91-442 ng/mL
23-25 years: 66-346 ng/mL
26-30 years: 60-329 ng/mL
31-35 years: 54-310 ng/mL
36-40 years: 48-292 ng/mL
41-45 years: 44-275 ng/mL
46-50 years: 40-259 ng/mL
51-55 years: 37-245 ng/mL
56-60 years: 34-232 ng/mL
61-65 years: 33-220 ng/mL
66-70 years: 32-209 ng/mL
71-75 years: 32-200 ng/mL
76-80 years: 33-192 ng/mL
81-85 years: 33-185 ng/mL
86-90 years: 33-179 ng/mL
> or=91 years: 32-173 ng/mL

Females:
0-11 months: 14-192 ng/mL
1 year: 23-243 ng/mL
2 years: 28-256 ng/mL
3 years: 31-249 ng/mL
4 years: 33-237 ng/mL
5 years: 36-234 ng/mL
6 years: 39-246 ng/mL
7 years: 44-279 ng/mL
8 years: 51-334 ng/mL
9 years: 61-408 ng/mL
10 years: 73-495 ng/mL
11 years: 88-585 ng/mL
12 years: 104-665 ng/mL
13 years: 120-719 ng/mL
14 years: 136-729 ng/mL
15 years: 147-691 ng/mL
16 years: 153-611 ng/mL

17 years: 149-509 ng/mL
18-22 years: 85-370 ng/mL
23-25 years: 73-320 ng/mL
26-30 years: 66-303 ng/mL
31-35 years: 59-279 ng/mL
36-40 years: 54-258 ng/mL
41-45 years: 49-240 ng/mL
46-50 years: 44-227 ng/mL
51-55 years: 40-217 ng/mL
56-60 years: 37-208 ng/mL
61-65 years: 35-201 ng/mL
66-70 years: 34-194 ng/mL
71-75 years: 34-187 ng/mL
76-80 years: 34-182 ng/mL
81-85 years: 34-177 ng/mL
86-90 years: 33-175 ng/mL
> or =91 years: 25-179 ng/mL

Tanner Stage reference ranges:
Males
Stage I: 81-255 ng/mL
Stage II: 106-432 ng/mL
Stage III: 245-511 ng/mL
Stage IV: 223-578 ng/mL
Stage V: 227-518 ng/mL

Females
Stage I: 86-323 ng/mL
Stage II: 118-451 ng/mL
Stage III: 258-529 ng/mL
Stage IV: 224-586 ng/mL
Stage V: 188-512 ng/mL

Tanner Stage reference source: Bindlingmaier M, Friedrich N, Emeny RT, et al. Reference intervals for insulin-like growth factor-1 (igf-i) from birth to senescence: results from a multicenter study using a new automated chemiluminescence IGF-I immunoassay conforming to recent international recommendations. J Clin Endocrinol Metab. 2014;99(5):1712-1721

Note: Puberty onset (transition from Tanner stage I to Tanner stage II) occurs for boys at a median age of 11.5 (+/-2) years and for girls at a median age of 10.5 (+/-2) years. There is evidence that it may occur up to 1 year earlier in obese girls and in African American girls. For boys, there is no definite proven relationship between puberty onset and body weight or ethnic origin. Progression through Tanner stages is variable. Tanner stage V (young adult) should be reached by age 18.

INSULIN-LIKE GROWTH FACTOR-BINDING PROTEIN 3
1-7 days: < or =0.7 mcg/mL
8-14 days: 0.5-1.4 mcg/mL
15 days-11 months: Unavailable
1 year: 0.7-3.6 mcg/mL
2 years: 0.8-3.9 mcg/mL
3 years: 0.9-4.3 mcg/mL
4 years: 1.0-4.7 mcg/mL
5 years: 1.1-5.2 mcg/mL
6 years: 1.3-5.6 mcg/mL
7 years: 1.4-6.1 mcg/mL
8 years: 1.6-6.5 mcg/mL
9 years: 1.8-7.1 mcg/mL
10 years: 2.1-7.7 mcg/mL
11 years: 2.4-8.4 mcg/mL
12 years: 2.7-8.9 mcg/mL
13 years: 3.1-9.5 mcg/mL
14 years: 3.3-10 mcg/mL
15 years: 3.5-10 mcg/mL
16 years: 3.4-9.5 mcg/mL
17 years: 3.2-8.7 mcg/mL
18 years: 3.1-7.9 mcg/mL
19 years: 2.9-7.3 mcg/mL
20 years: 2.9-7.2 mcg/mL
21-25 years: 3.4-7.8 mcg/mL
26-30 years: 3.5-7.6 mcg/mL
31-35 years: 3.5-7.0 mcg/mL
36-40 years: 3.4-6.7 mcg/mL
41-45 years: 3.3-6.6 mcg/mL
46-50 years: 3.3-6.7 mcg/mL
51-55 years: 3.4-6.8 mcg/mL
56-60 years: 3.4-6.9 mcg/mL
61-65 years: 3.2-6.6 mcg/mL
66-70 years: 3.0-6.2 mcg/mL
71-75 years: 2.8-5.7 mcg/mL
76-80 years: 2.5-5.1 mcg/mL
81-85 years: 2.2-4.5 mcg/mL

Tanner Stages:
Males
Stage I: 1.4-5.2 mcg/mL
Stage II: 2.3-6.3 mcg/mL

Stage III: 3.1-8.9 mcg/mL
Stage IV: 3.7-8.7 mcg/mL
Stage V: 2.6-8.6 mcg/mL

Females
Stage I: 1.2-6.4 mcg/mL
Stage II: 2.8-6.9 mcg/mL
Stage III: 3.9-9.4mcg/mL
Stage IV: 3.3-8.1 mcg/mL
Stage V: 2.7-9.1 mcg/mL

Note: Puberty onset, ie, the transition from Tanner stage 1 (prepubertal) to Tanner stage 2 (early pubertal), occurs for girls at a median age of 10.5 (+/-2) years and for boys at a median age of 11.5 (+/-2) years. There is evidence that it may occur up to 1 year earlier in obese girls and in African American girls. By contrast, for boys there is no definite proven relationship between puberty onset and body weight or ethnic origin. Progression through Tanner stages is variable. Tanner stage 5 (young adult) should be reached by age 18.

Interpretation

Both insulin-like growth factor 1 (IGF1) and insulin-like growth factor binding protein 3 (IGFBP3) measurements can be used to assess growth hormone (GH) excess or deficiency. However, for all applications, IGF1 measurement has generally been shown to have superior diagnostic sensitivity and specificity and should be used as the primary test. In particular, in the diagnosis and follow-up of acromegaly and gigantism, IGFBP3 measurement adds little, if anything, to IGF1 testing.

The combination of IGF1 and IGFBP3 measurements might offer some benefits over either analyte alone in the diagnosis of GH deficiency and resistance, and in the monitoring of recombinant human GH (rhGH) therapy.

Serum IGF1 and IGFBP3 concentrations below the 2.5th percentile (standard deviation score, Z-score of <-2) for age are consistent with GH deficiency or severe GH resistance, but patients with incomplete GH deficiency or mild-to-moderate GH resistance may have levels within the reference range. In GH deficiency, GH levels may also be low and can show suboptimal responses in stimulation tests (eg, exercise, clonidine, arginine, ghrelin, growth hormone-releasing hormone, insulin-induced hypoglycemia), while in severe GH resistance, GH levels might be substantially elevated. However, dynamic GH testing is not always necessary for diagnosis. If it is undertaken, it should be performed and interpreted in endocrine testing centers under the supervision of a pediatric or adult endocrinologist.

The aim of both pediatric and adult GH replacement therapy is to achieve IGF1 and IGFBP3 levels within the reference range, ideally within the middle-to-upper third. Higher levels are rarely associated with any further therapeutic gains but could potentially lead to long-term problems of GH excess.

Elevated IGF1 and IGFBP3 levels support the diagnosis of acromegaly or gigantism in individuals with appropriate signs or symptoms. In successfully-treated patients, both levels should be within the normal range, ideally within the lower third. In both diagnosis and follow-up, IGF1 levels correlate better with clinical disease activity than IGFBP3 levels.

After transsphenoidal removal of pituitary tumors in patients with acromegaly, IGF-I concentration starts to decrease and returns to normal levels in most patients postoperatively by the fourth day.

Persons with anorexia or malnutrition have low values of IGF1. IGF1 is a more sensitive indicator than prealbumin, retinol-binding protein, or transferrin for monitoring nutritional repletion.

Cautions

Insulin-like growth factor 1 (IGF1) and insulin-like growth factor-binding protein 3 (IGFBP3) reference values are highly age dependent, and results must always be interpreted within the context of the patient's age.

During normal pregnancy, serum IGF1 increases, on average, almost 2-fold (range approximately 1.1-fold to approximately 4-fold) over prepregnancy baseline concentrations; however, reference values for this population have not been formally established at our institution.

Discrepant IGF1 and IGFBP3 results can sometimes occur due to liver and kidney disease; however, this is uncommon. Such results should alert laboratories and physicians to the possible occurrence of a preanalytical or analytical error.

Currently, IGF1 or IGFBP3 cannot be reliably used as risk indicators or prognostic markers in breast, colon, prostate, or lung cancer.

IGF1 assays exhibit significant variability among platforms and manufacturers. Direct comparison of results obtained by different assays is problematic. If IGF1 and IGFBP3 are being used for serial monitoring, reestablishment of the patient's baseline levels is preferred if assays are changed.

Several amino-acid benign alterations within *IGF1* have been discovered. At least 4 of these are known to result in IGF1 isoforms with diminished biological activity. IGF1 immunoassays vary in their ability to detect these reduced-function variants. Detection of the variant proteins may result in an overestimation of functionally active IGF1 in an affected patient. By contrast, a mass spectrometry (MS)-based IGF1 assay can usually selectively detect the active IGF1 isoforms. However, there might be as yet unknown functionally different variants of IGF1, which even MS cannot distinguish from wildtype (normal) IGF1.

Since the IGFBP3 assay is an immunometric assay, heterophile antibody interferences can rarely cause erroneous results, usually false-high. Heterophile antibodies in human serum can react with the immunoglobulins included in the assay components causing interference with immunoassays. Specimens from patients with autoimmune diseases or from individuals routinely exposed to animals or animal serum products can demonstrate this type of interference, potentially causing an anomalous result. The assay reagents have been formulated to minimize the risk of such interference; however, rare interactions can occur. For diagnostic purposes, the results obtained from this assay should always be used in combination with the clinical examination, patient medical history, and other findings.

Clinical Reference

1. Wetterau L, Cohen P. Role of insulin-like growth factor monitoring in optimizing growth hormone therapy. J Ped Endocrinol Metab. 2000;13:1371-1376
2. Granada ML, Murillo J, Lucas A, et al. Diagnostic efficiency of serum IGF-1, IGF-binding protein-3 (IGFBP-3),

IGF/IGFBP-3 molar ratio and urinary GH measurements in the diagnosis of adult GH deficiency: importance of an appropriate reference population. Eur J Endocrinol. 2000;142:243-253
3. Parama C, Fluiters E, de la Fuente J, et al. Monitoring of treatment success in patients with acromegaly: the value of serum insulin-like growth factor binding protein-3 and serum leptin measurements in comparison to plasma insulin-like growth factor 1 determination. Metabolism. 2001;50:1117-1121
4. Monzavi R, Cohen P. IGFs and IGFBPs: role in health and disease. Best Pract Res Clin Endocrinol Metab. 2002;16:433-447
5. Boquete HR, Sobrado PG, Fideleff HL, et al. Evaluation of diagnostic accuracy of insulin-like growth factor (IGF)-1 and IGF-binding protein-3 in growth hormone-deficient children and adults using ROC plot analysis. J Endocrinol Metab. 2003;88:4702-4708
6. Brabant G. Insulin-like growth factor-I: marker for diagnosis of acromegaly and monitoring the efficacy of treatment. Eur J Endocrinol. 2003;148:S15-S20
7. Boscato LM, Stuart MC. Heterophilic antibodies: a problem for all immunoassays. Clin Chem. 1988;34:27-33
8. Maus A, Kemp J, Milosevic D, et al. Center of mass calculation in combination with MS/MS allows robust identification of single amino acid polymorphisms in clinical measurements of insulin-like growth factor-1. J Proteome Res. 2020;19(1):186-193. doi:10.1021/acs.jproteome.9b00494

Performance

Method Description

Insulin-Like Growth Factor 1:
Stable isotope labeled internal standard is added to patient samples. Insulin-like growth factor 1 (IGF1) is then extracted by selective precipitation. The extracted samples are analyzed by liquid chromatography mass spectrometry. This is a laboratory-developed mass spectrometry test, calibrated against the First World Health Organization International Standard for IGF1 (02/254).(Unpublished Mayo method)

Insulin-Like Growth Factor-Binding Protein 3:
The IMMULITE 2000 IGFBP3 (insulin-like growth factor-binding protein 3) is a solid-phase, enzyme-linked chemiluminescent immunoassay based on murine monoclonal antibodies. The patient sample and alkaline phosphatase-conjugated anti-IGFBP3 antibodies are simultaneously incubated with an antibody-coated bead. During this time, IGFBP3 in the sample forms an antibody sandwich complex that binds to the streptavidin on the bead. Unbound enzyme conjugate is then removed by washing, after which substrate is added. The chemiluminescent substrate, a phosphate ester of adamantyl dioxetane, undergoes hydrolysis in the presence of alkaline phosphatase to yield an unstable intermediate. The continuous production of this intermediate results in the sustained emission of light. The photon output is directly proportional to the concentration of IGFBP-3 in the sample.(Package insert: IMMULITE 2000 IGFBP-3. Siemens Healthcare Diagnostics; PIL2KGB-15. 03/2018)

PDF Report

No

Day(s) Performed

Monday through Saturday
Results reported: Monday through Friday

Report Available
4 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
See Individual Test IDs

CPT Code Information
83520
84305

LOINC® Information

Test ID	Test Order Name	Order LOINC® Value
IGFGP	IGF-1 LC/MS, IGFBP-3 Growth Panel	In Process

Result ID	Test Result Name	Result LOINC® Value
IGFB3	IGFBP-3, S	2483-6
62750	IGF-1, LC/MS, S	2484-4
35781	Z-score	73561-3