

COMMUNIQUE

IMPROVING PATIENT CARE THROUGH ESOTERIC LABORATORY TESTING

VOLUME 31, NO. 3

Insulin-like Growth Factor-1 (IGF-1)—The First-line Test for Assessing Excess Growth Hormone

Insulin-like growth factors, including insulin-like growth factor-1 (IGF-1) and insulin-like growth factor binding protein-3 (IGFBP-3), belong to a family of related peptides that mediate many of the biological actions of growth hormone (GH). IGF-1 testing is a valuable diagnostic and disease status-monitoring tool for patients with acromegaly. IGF-1 testing is often superior to GH measurements, because IGF-1 secretion patterns show less variability than GH secretion.

Growth Hormone

Growth hormone (GH), formally called *somatotropin*, promotes and stimulates growth. It also helps maintain normal protein synthesis in bone, muscle and cartilage, and plays a role in normal carbohydrate and lipid metabolism. While GH produces some somatic effects directly, many are mediated through IGF-1. GH stimulates the production of IGF-1 and IGFBP-3 protein in the liver and other tissues.

GH is secreted from the pituitary into the blood where it circulates until it contacts cells that have GH receptors; it then binds to the GH receptors and mediates IGF-1 production through transcription factors. GH is primarily regulated by hypothalamic factors, with growth hormone-releasing hormone (GHRH) stimulating secretion and somatostatin suppressing it (Figure 1).

GH has a very short half-life ($t_{1/2}$) of 30 minutes. In normal individuals, most (95%) GH secretion occurs in pulses (Figure 2). Most secretion occurs during the deep stages of sleep, and daytime levels in resting individuals are generally low or undetectable. However, GH secretion is also influenced by stress, exercise, caloric intake, gender, and age. In concert, the short $t_{1/2}$, pulsatile secretion, diurnal variation, and effects of environmental secretion stimuli make the interpretation of GH measurements in individuals difficult. This led to the use of IGF-1 testing, whose levels are directly influenced by GH.

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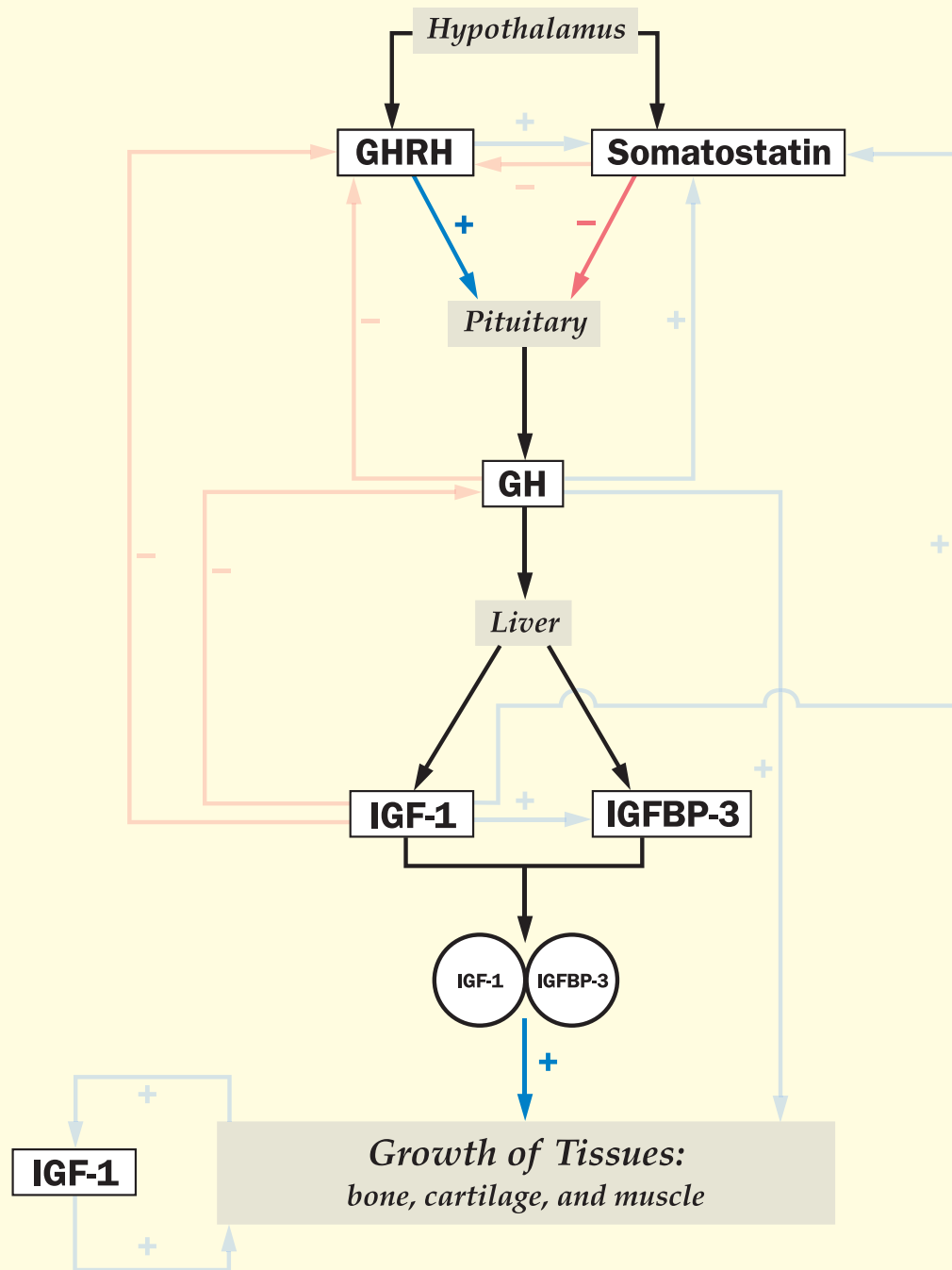


Figure 1. Regulation of the GH/IGF-1 axis.

Insulin-like Growth Factor-1

Insulin-like growth factor-1 (IGF-1), formerly called *somatomedin*, is a single chain polypeptide comprised of 70 amino acids. As its name implies, it has structural and functional homology to insulin. IGF-1 production is primarily regulated by GH. IGF-1 in turn inhibits the release of GHRH at the level of the hypothalamus, thus decreasing GH levels through an endocrine negative feedback loop (Figure 1).

Most (approximately 80%) circulating IGF-1 is made in the liver, and released into the bloodstream where it acts in endocrine fashion on other tissues. IGF-1 is also produced locally in many other tissues, in particular epiphyseal cartilage and skeletal muscle. Most of the latter fraction of IGF-1 acts locally in a paracrine fashion and does not circulate systemically. Most (approximately 80%) circulating IGF-1 is bound to IGFBP-3, <1% is unbound, and the remainder is bound to other IGF-binding proteins.¹ Noncomplexed IGF-1 and IGFBP-3 have short $t_{1/2}$ s of 10 and 30 to 90 minutes, respectively, while the IGF-1/IGFBP-3 complex is cleared with a

much longer $t_{1/2}$ of 16 hours.¹ Because IGF-1 production is regulated by GH and nearly all (99%) IGF-1 is bound, its measurement allows a stable and integrated view of GH secretion and tissue-level activity, circumventing the problems of pulsatile secretion and diurnal variation that bedevil serum GH measurements (Figure 2). IGF-1 levels are also influenced by nutritional intake, thyroxine, chronic illness, and age most of all. IGF-1 levels are lower in children, peak at puberty, and gradually decline throughout adulthood. IGF-1 reference ranges must therefore always be interpreted within the context of the patient's age.

Insulin-like Growth Factor Binding Protein-3

Insulin-like growth factor binding protein-3 (IGFBP-3), is comprised of 264 amino acids and is produced by the liver. It is the most abundant member of the insulin-like growth factor binding protein family. IGFBP-3 mediates transport and controls bioavailability and $t_{1/2}$ of insulin-like growth factors, especially IGF-1. Production is primarily regulated by GH and IGF-1, and the secretion patterns of IGFBP-3 and IGF-1 mimic each other.

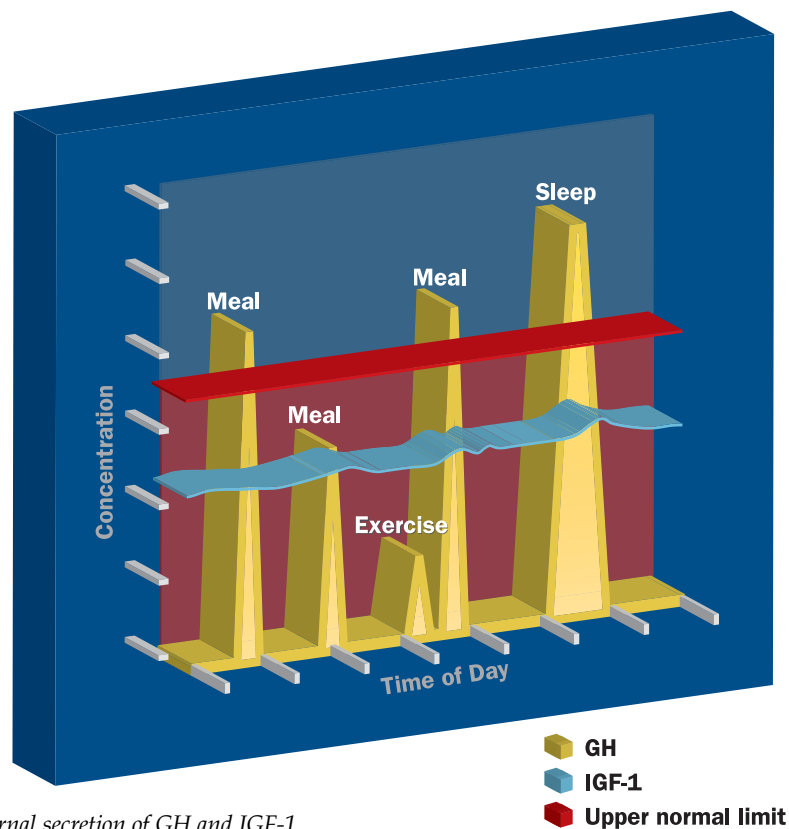


Figure 2. Normal variability of diurnal secretion of GH and IGF-1.

Utilization of IGF-1 Testing for Diagnosis and Monitoring of Acromegaly

Acromegaly is a disorder of excess GH production that is characterized by bone and soft tissue overgrowth, coarse facial features and large hands and feet. Patients may also experience the complications of cardiovascular disease and diabetes mellitus, as well as various other signs and symptoms (Table 1). Mortality is 2-4 times higher in acromegaly patients than the normal population, mainly as a result of cardiovascular disease, but successful treatment abolishes this risk.^{2,4} Timely diagnosis and treatment is crucial to optimally improving quality of life and to normalizing life expectancy.

Most (95%) cases of acromegaly are caused by benign GH-secreting pituitary adenomas (Figure 3, Table 1). Rarely, it may be caused by malignant pituitary tumors or by tumors that secrete GHRH. Drug-induced acromegaly, usually much milder, is also occasionally observed, due to therapeutic GH and IGF-1 use, as well as secondary to unconventional or illegal use of GH and IGF-1 to slow the aging process or to enhance athletic performance (See accompanying Ask Us Section, page 12).

Acromegaly

Signs and Symptoms

Local Tumor Effects

- visual field loss
- cranial nerve palsies

Effects of Systemic GH Excess

- coarse facial features
- headache
- fatigue
- thick skin
- acanthosis nigricans
- joint thickening
- carpal tunnel syndrome
- cardiovascular disease (most commonly hypertension)
- excessive sweating
- unusual increase in hat, ring, or shoe size
- gaps between teeth
- diabetes mellitus
- sleep apnea

Causes

GH-secreting Pituitary Tumors

- benign adenoma*
- carcinoma

GHRH-secreting Tumors

Exogenous Sources of GH

Genetic Causes

- multiple endocrine neoplasia Type I
- McCune-Albright syndrome
- Carney's complex

*most common cause of acromegaly

Table 1. Clinical characteristics and causes of acromegaly.

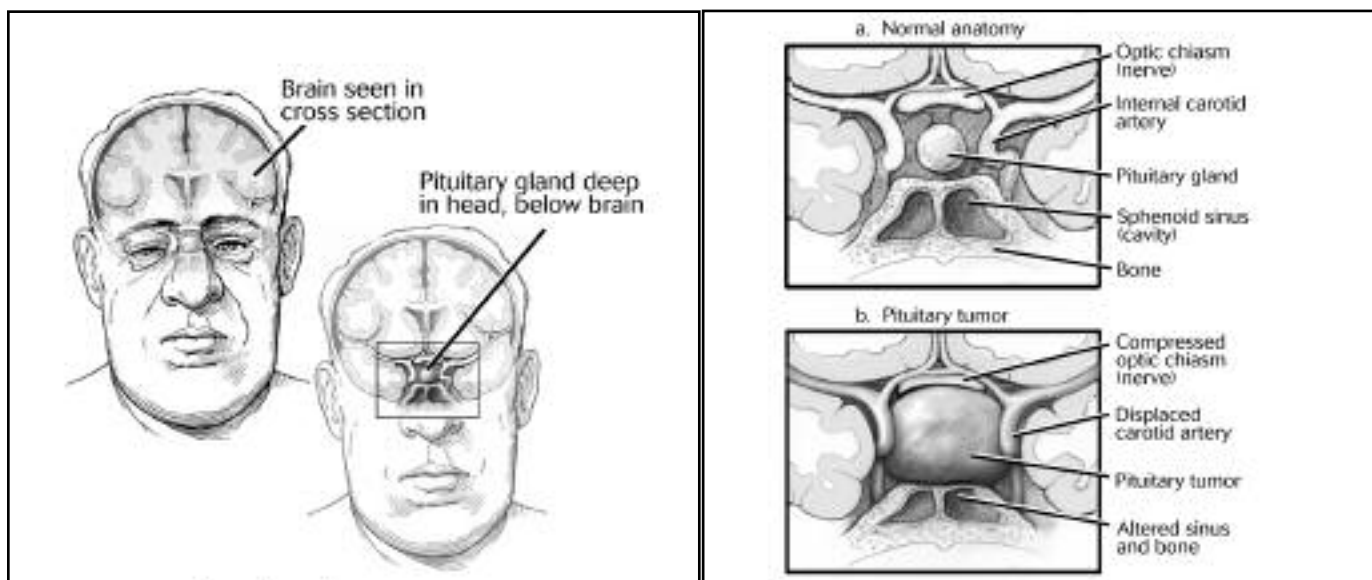


Figure 3. GH-secreting pituitary tumor (acromegaly).

Diagnosis

When excess GH develops before puberty, the patient presents with gigantism. However, when excess GH develops after puberty, clinical diagnosis becomes more difficult and is often delayed by up to 10 years.

IGF-1 testing is recommended as the best initial screening test for all patients suspected of having acromegaly (Figure 4).^{2,4} IGF-1 is consistently elevated in acromegaly patients, and, as described above, has a less variable serum concentration than GH. Because it provides an integrative measurement of GH activity, it also is a very sensitive indicator of minimal chronic increases in GH secretion. IGF-1 also is the best indicator of clinical disease activity both during initial assessment and later to assess and monitor treatment. Measurement of IGF-1 requires only a random blood specimen. With rare exceptions, a serum IGF-1 level in the normal range excludes acromegaly. Once established that a patient has elevated IGF-1, it is important to exclude causes of elevated GH other than a pituitary tumor.

GH Testing is of Limited Clinical Utility in Acromegaly Diagnosis

Random GH testing is not recommended for the diagnosis of acromegaly. Nearly 30% of acromegaly patients will have random GH levels within the normal reference range. Of these 20% to 50% will, however, have elevated IGF-1 levels.⁵ Conversely, many normal individuals may have random GH measurements well above the upper limit of the reference range following exercise or various other stimuli. The 24-hour mean integrated GH test was in the past thought to be better than random GH measurements. However, the test is impractical because it is costly, requires an inpatient hospital stay, generates >70 samples to be tested, and is time consuming for the patient and medical staff.⁴

Oral Glucose Tolerance Test with Measurement of GH Suppression (OGTT GH)

If patients suspected of having acromegaly do not have clearly elevated IGF-1 levels, then OGTT GH testing may provide additional diagnostic benefit, especially in adolescent patients.^{2,3} Normally, glucose suppresses insulin, which in turn suppresses GH.

However, GH-producing tumors are not suppressed by insulin. OGTT GH is performed by giving 75 g of glucose orally and sampling for glucose and GH levels at 0, 30, 60, 90, and 120 minutes after administration of glucose.²

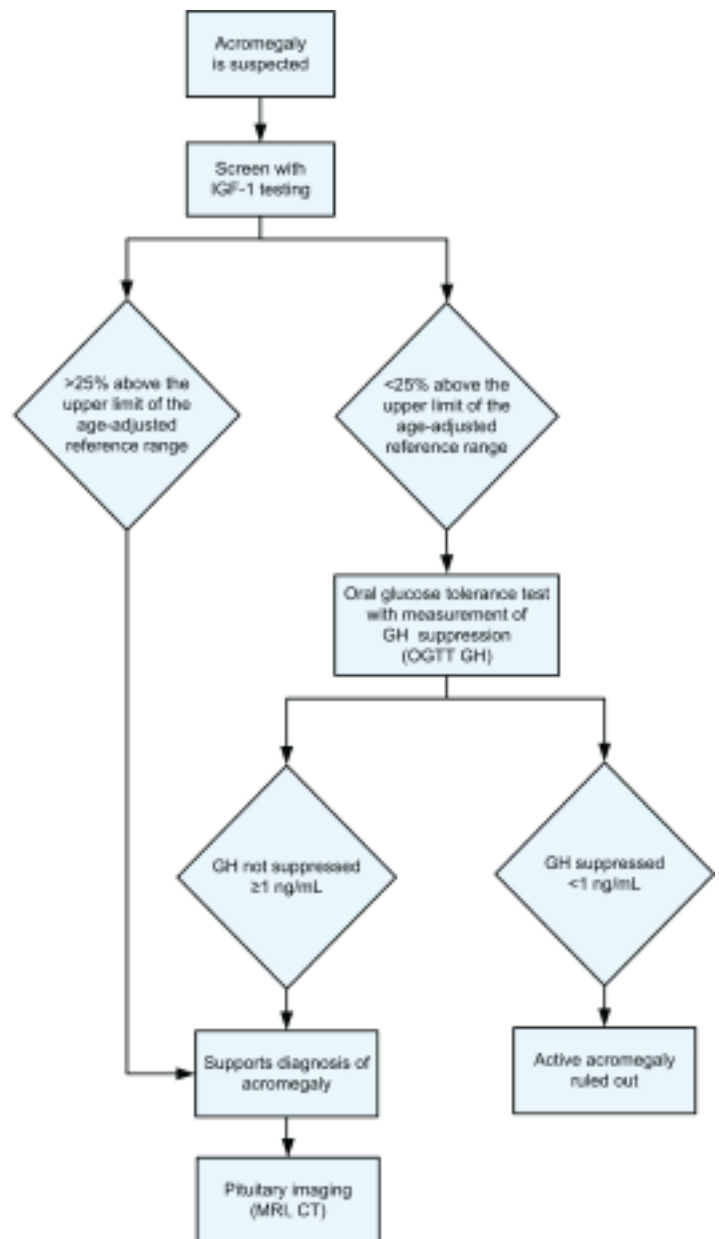


Figure 4. Algorithm for diagnosis of acromegaly.



since IGF-1 also mediates IGFBP-3 levels. Additionally, IGFBP-3 testing is not as sensitive as IGF-1 at detecting GH in excess. In acromegaly patients, IGFBP-3 levels do not increase as much as IGF-1 levels, and they sometimes overlap with normal patient values. This is likely because serum IGFBP-3 levels are regulated by other growth factors independent of the influence of excess GH. Thus IGFBP-3 is not recommended for routine use, but in cases where OGTT GH and IGF tests are discordant, it may be a useful adjunct test.³

Other Tests NOT Recommended

Previously, thyrotropin-releasing hormone (TRH), GHRH, gonadotropin-releasing hormone (GnRH), antilymphocyte serum, free IGF-1, urinary GH, 24-hour mean integrated GH test, and GH stimulatory tests have all been advocated for the diagnosis of acromegaly. None of these tests offers any advantages over IGF-1 testing with or without OGTT GH suppression testing.⁴

If the serum GH levels are ≥ 1 ng/mL (2.6 mU/L) during OGTT suppression testing (ie, nonsuppressed), it supports the diagnosis of acromegaly.^{2,4,6} Failure to suppress OGTT GH levels below 1 ng/mL, combined with abnormally elevated IGF-1 levels, is diagnostic of acromegaly.^{2,4} When monitoring patients serially, using the same assay whenever possible is important because of the variability between different assays. If the assay method is changed, the patient should be rebaselined.

When IGF-1 and OGTT GH tests are employed together to diagnose acromegaly, they have a predictive value of 95%.¹ However, OGTT GH suppression testing should primarily be used as an adjunct to IGF-1 measurements, as approximately 20% of patients with acromegaly will have a normal OGTT GH suppression test, while their IGF-1 is elevated.^{2,4} Additionally, several factors can cause false-positive OGTT GH test results, including adolescence, diabetes mellitus, liver disease, renal disease, and anorexia nervosa.^{3,4}

IGFBP-3 Testing

No data indicates that IGFBP-3 is superior to IGF-1 testing, and IGF-1 testing is somewhat more direct



Treatment

Successful treatment lowers the mortality rate of patients with acromegaly to that of the normal population.^{2,4} While treatment will not reduce bone enlargement, it can prevent further enlargement, alleviate soft tissue excess (reducing hand and foot size), and reduce headaches, optic compression, and comorbidities associated with active acromegaly (sleep apnea, cardiomyopathy, hypertension, arthritis and diabetes mellitus). Treatment options include surgery, drug therapy, and radiation therapy, used singly or in combination.

Surgery

Surgery is the treatment of choice for acromegaly. The surgical cure rate for microadenomas (<1 cm) is 80% to 91% and less than 30% to 50% for macroadenomas.⁴ Postoperative complications (<5%) such as vision problems, spinal fluid leak, meningitis, postoperative pituitary insufficiency, and brain damage are more common in macroadenomas.⁷

Drug Therapy

Drug therapy may be recommended as a pretreatment before surgery, for patients who are not cured by surgery, or for patients who are too ill to undergo surgery.^{2,7} Currently available drug therapies include somatostatin analogs, dopamine agonists, and GH receptor antagonists.

Somatostatin analogs are the primary drug of choice for treating acromegaly.^{2,7} They work by binding somatostatin receptors on the tumor, thus blocking GH secretion. Somatostatin analogs may be effective at normalizing IGF-1 levels in over half of patients and alleviating symptoms of acromegaly in nearly three fourths of patients.²

Dopamine agonists inhibit secretion of GH by stimulating dopaminergic receptors on the tumor. Dopamine agonists are effective at lowering GH and IGF-1 serum levels in approximately 10% to 35% of patients, and are most commonly used for treating patients with tumors that secrete both GH and

prolactin.^{2,7} Suppression of GH and IGF-1 levels by dopamine agonists may take up to 3 months, and patients achieve normalization of IGF-1 and GH only rarely.

GH receptor antagonists are a relatively new category of acromegaly drugs. They bind with high affinity to GH receptors and block GH production at the tissue level. Clinical trials have demonstrated normalization of serum IGF-1 levels in more than 90% of acromegaly patients.² However, long-term effects of these drugs are unknown. GH receptor antagonist therapy makes monitoring of GH difficult or impossible, because of assay cross-reactivity.

Radiation Therapy

Radiation therapy is commonly used to treat patients whose GH levels are not adequately reduced by surgical or medical therapy.^{2,7} Approximately 90% of radiotherapy-treated patients achieve random GH levels of <5 µg/L (reference values for normal males: ≤1.5 ng/mL; females: ≤4.0 ng/mL), although it may take many years to reach this level.^{2,4} Complete cure is much less common. The most common long-term side effect is hypopituitarism (ie, infertility, hypogonadism), which occurs in over half of patients usually 5 to 10 years after radiation treatment, but can also occur later. Patients who are cured by radiation therapy are at increased risk of pituitary failure.

Monitoring Therapy

IGF is an important indicator of disease activity in acromegaly. The standard treatment recommendation is to treat patients until their serum GH concentrations, as measured by OGTT, are <1 µg/L and their IGF-1 levels are within the 95% confidence interval for their age.^{4,6,7} More recently, IGF-1 target levels in the lower third of the age-adjusted reference interval have been advocated (Figure 5). Most (83% to 90%) acromegaly patients can achieve normal IGF-1 levels, but fewer will achieve levels in the lower third of the reference range.⁸ It is currently uncertain whether individuals who do not achieve this newer goal have worse outcomes.

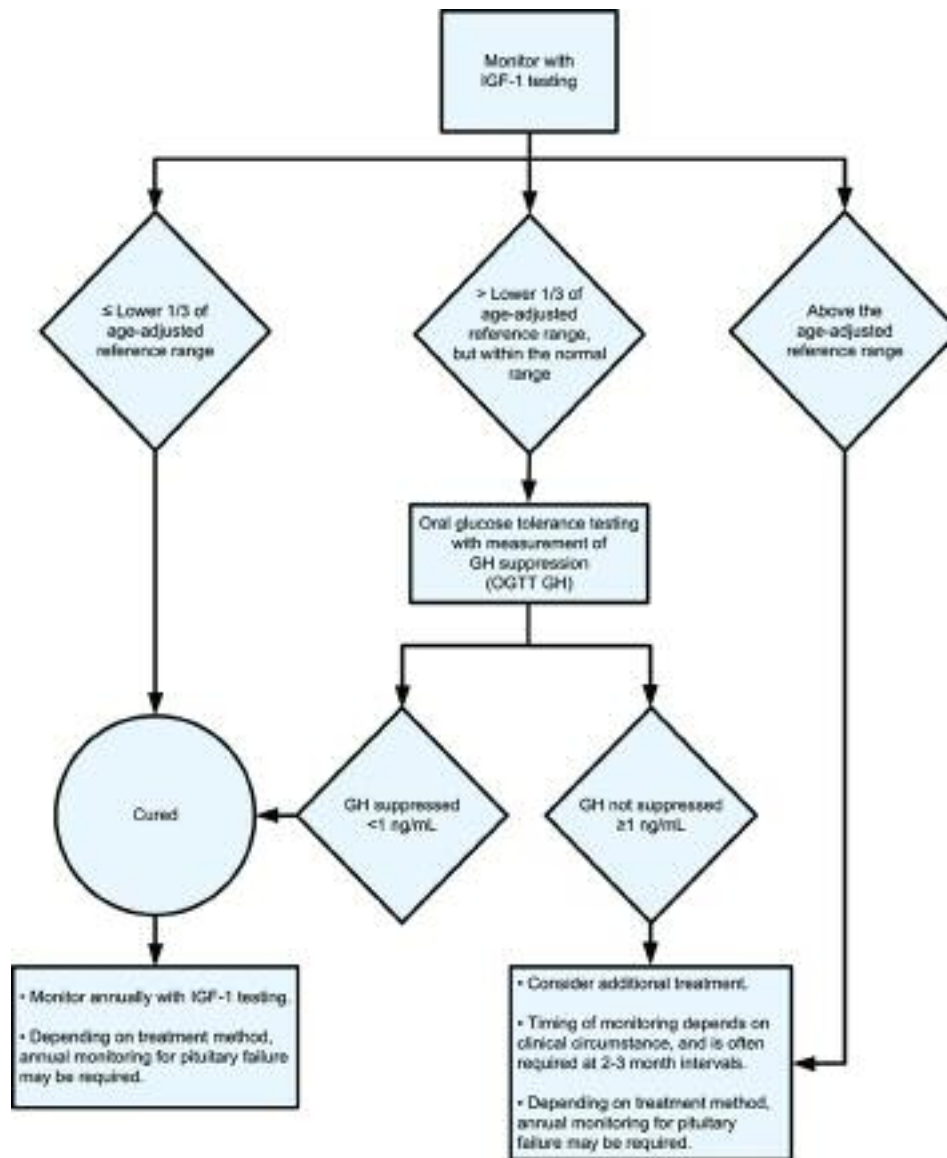


Figure 5. Algorithm for monitoring acromegaly treatment and disease activity.

Most published studies have demonstrated that IGF-1 is a more sensitive indicator of persistent disease activity than is GH.¹ To ensure optimal IGF-1 and GH levels are sustained, all patients with acromegaly require lifelong monitoring.^{3,4} IGF-1 and OGTT GH levels should be measured 3 months after surgery.³ Up to one third of acromegaly patients will have elevated IGF-1 levels and require additional therapy. Additionally, low but nonsuppressible OGTT GH levels combined with normal IGF-1 levels occur in some patients after surgical treatment. If these patients are symptomatic, additional therapy is warranted; if they are asymptomatic, they should be monitored carefully.²

IGF-1 and/or OGTT GH levels should also be measured 2 to 3 months after the start of medical therapy to assess dose adequacy.⁷ For monitoring treatment with GH-receptor antagonists, IGF-1 is the only suitable test, since blocking the GH receptor leads to increased GH serum concentrations and the drug cross-reacts in the assay.³ IGF-1 can be tested at 4-week intervals following medication dosage changes, although maximal steady state responses may take longer in some patients.¹ Once effective dosages have been determined, annual testing of IGF-1 and OGTT GH is recommended for patients taking somatostatin analogs or dopamine agonists. Patients taking GH receptor antagonists should undergo IGF-1 testing and radiographic studies every 6 months to assess disease activity and monitor tumor size.³

IGF-1 and OGTT GH should be measured annually to monitor effects of radiation therapy.³ During annual follow-up, pituitary function should also be assessed because of the high risk of iatrogenic hypopituitarism. This would usually include measurement of luteinizing hormone (LH), follicle-stimulating hormone (FSH), thyroid-stimulating hormone (TSH), free thyroxine, and cortisol testing (morning serum cortisol and ACTH 1-24 stimulation testing), as well as estradiol in women and testosterone in men.

Conclusions

Diagnosis of acromegaly in adult patients is difficult and is often made years after the onset of disease. Timely diagnosis can substantially reduce symptoms,

comorbidities, and mortality associated with acromegaly. IGF-1 testing is cost-effective, sensitive, specific, and a reliable screening tool for acromegaly; IGF-1 testing also plays an important role in monitoring treatment strategies and disease activity in acromegaly patients. Available tests include:

- #15867 Insulin-Like Growth Factor 1, Serum
- #83357 Insulin-Like Growth Factor 1 (IGF-1) and Insulin-Like Growth Factor Binding Protein 3 (IGFBP-3) Growth Panel
- #8688 Growth Hormone, Serum

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Test Updates

Ashkenazi Jewish Mutation Analysis Panel Specimen Requirements Update

The specimen requirements for #86329 Ashkenazi Jewish Mutation Analysis Panel has changed. The new specimen requirements follow:

“Molecular Genetics - Biochemical Disorders Patient Information Sheet” (Supply T527) is required for all orders. If not ordering electronically, please submit the above information sheet along with a “Molecular Genetics Request Form” (Supply T245) with the specimen.

Specimen must arrive within 72 hours of collection.

Draw 2 full, yellow-top (ACD) tubes, and send ACD whole blood in original VACUTAINERS. Invert several times to mix blood. Forward unprocessed whole blood promptly at ambient temperature.

Note: Patient education brochure (Supply T561) is available upon request.

New Mayo Supply Item for Collection of Bronchial Brushing

MML is please to announce the availability of CytoLyt solution centrifuge tubes. This item, T564 CytoLyt Solution, is used for the transport of a bronchial brush containing exfoliated cells that have been collected during a bronchoscopy procedure. The brush is placed directly into the CytoLyt solution centrifuge tube for transport to the laboratory. When the specimen reaches MML, the cellular material is harvested from the brush and a cell pellet is prepared by centrifugation. The pellet is resuspended and preserved in PreservCyt® solution to preserve cellular integrity, then processed using the ThinPrep 2000 processor. Specimens are then stained and microscopically analyzed by both a cytotechnologist and pathologist. Please contact MML client services at 800-533-1710 to order this item.



Supply item T564 CytoLyt solution centrifuge tubes.

2006 EDUCATION CALENDAR

Upcoming Education Conferences . . .

Phlebotomy Conference 2006: Do You Speak Phlebotomy?

March 30-31, 2006

Siebens Building • Mayo Clinic, Rochester, MN

Quality Phlebotomy: Back to the Basics

April 11, 2006

Inverness Hotel & Conference Center • Englewood, CO

Practical Spirometry

April 13-14, 2006

Kahler Heritage Hall, Kahler Hotel • Rochester, MN

13th International Surgical Pathology Symposium

May 2-5, 2006

Hotel Maggior Consiglio • Treviso, Italy

Integration Through Community Laboratory Insourcing

May 3-5, 2006

Disney Coronado Springs Resort • Orlando, FL

Bleeding and Thrombosing Diseases - Wet Workshop

August 2, 2006

The Kahler Grand Hotel • Rochester, MN

Bleeding and Thrombosing Diseases Conference

August 3-4, 2006

The Kahler Grand Hotel • Rochester, MN

Practical Surgical Pathology

September 14-16, 2006

Siebens Building • Mayo Clinic, Rochester, MN

State-of-the-Art Thrombophilia

September 21-23, 2006

Siebens Building • Mayo Clinic, Rochester, MN

Quality Phlebotomy: Back to the Basics

October 2, 2006

Hilton Dallas/Park Cities • Dallas, TX

Practical Spirometry

October 12-13, 2006

Radisson Hotel & Suites • Chicago, IL

Real-Time PCR for the Clinical Microbiology Laboratory

October 26-27, 2006

Siebens Building • Mayo Clinic, Rochester, MN

Practical Spirometry

November 14-15, 2006

Siebens Building • Mayo Clinic, Rochester, MN

Interactive Satellite Programs . . .

New Assessment and Management Guidelines for the Patient with Chronic Kidney Disease

March 14, 2006

Presenters: Timothy S Larson MD

Suzanne M Norby MD

Diagnosis and Treatment of Community Acquired Pneumonia

April 11, 2006

Presenters: Franklin R Cockerill III MD

Robert J Stroebel MD

The Laboratory Approach to the Child With Possible Immunodeficiency

May 24, 2006

Presenter: Thomas G Boyce MD

Genomics and Proteomics: An Update

September 12, 2006

Presenter: David B Schowalter MD, PhD

An Approach to Evaluation of Bleeding Disorders

October 3, 2006

Presenter: Rajiv K Pruthi MBBS

Update on Contemporary Pain Management of the Patient with Cancer

November 14, 2006

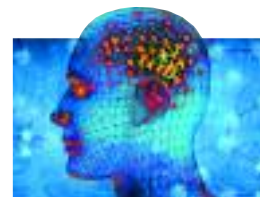
Presenters: Marc A Huntoon MD

Toby N Weingarten MD

Update on Cardiovascular Markers

December 12, 2006

Presenter: Allan S Jaffe MD



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ASK US

Question: Can IGF-1 testing be used to monitor GH therapy for antiaging and athletic performance enhancement?

Answer: To date there has been no clinical study evidence establishing the long-term efficacy of GH therapy for antiaging or athletic enhancement purposes. Some research has suggested that GH and IGF treatment may hold promise for maintaining health or restoring function to a number of organ systems, but the evidence is very preliminary. Unfortunately, the studies have generated a substantial amount of marketing promoting GH and IGF therapy to enhance athletic performance and to counter the effects of aging. Additionally, some entities are marketing GH and IGF as oral sprays or supplements despite the facts that only injectible forms are biologically active and no research evidence supports the claim that orally administered GH or IGF-1 is effective. Marketing GH use to counteract the effects of aging or to enhance athletic performance has been denounced by congressional committees, the Federal Trade Commission, and the National Institute on Aging.¹

FDA-approved use of GH therapy in adults

In 2003, the FDA approved recombinant GH

therapy for adults with severe growth hormone deficiency or acquired immunodeficiency syndrome (AIDS) wasting. Most importantly, the administration of GH or IGF therapy in adults is illegal except for conditions approved by the FDA, and penalties for improper use include prison sentences and substantial fines.¹

Safety concerns associated with GH and IGF-1 therapy in adults

To date, there is no clinical study evidence that has established the long-term safety of GH or IGF-1 therapy. Studies have demonstrated that GH therapy is associated with serious side effects including glucose intolerance, diabetes, edema, carpal tunnel syndrome, elevated triglyceride levels, intracranial hypertension, and joint and muscle pain. IGF-1 therapy is more risky than GH therapy, in particular, as it can lead to hypoglycemia. Another concern is that GH and IGF treatment may increase the growth of existing cancerous lesions.

Reference:

1. Perls TH, Reisman NR, Olshansky SJ: Provision or distribution of growth hormone for "antiaging": Clinical and legal issues. JAMA 2005;294(16):2086-2090



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MC2831-0306

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