

## Growth Hormone Deficiency

### Clinical Background

Growth hormone (GH) deficiency is usually acquired in adulthood and is not uncommon in childhood.

#### Childhood GH deficiency

- Epidemiology
  - Prevalence – not uncommon
  - Age – recognized by slow linear growth of <1 percentile
  - Sex – M>F
- Etiology
  - Idiopathic growth hormone deficiency
  - Inborn errors of the *POU1F1* gene
  - *PROP1* mutations
  - Growth hormone releasing hormone (*GHRH*) gene defects
    - Genetic insensitivity to GH
- Pathophysiology
  - GH is secreted by the anterior pituitary
  - Binding of GH to the transmembrane receptor leads to the production of insulin-like growth factor 1 (IGF-1) and insulin-like growth factor binding protein 3 (IGFBP-3)
  - Secreted in a pulsatile fashion, natural impetus for secretion is sleep (rises at night and sporadically during the day; may be related to meals)
  - GH levels increase in response to hypoglycemia
- Clinical Presentation
  - Short stature (defined as height >2 standard deviations below the mean), severe growth failure, delayed bone age
- Treatment
  - FDA indications for GH replacement
    - GH deficiency
    - No GH deficiency but other indications
      - Idiopathic short stature (ISS) – most controversial indication
      - Small for gestational age (SGA) infants
        - 90% SGA infants catch up in growth by age 2 and do not require GH supplementation
      - Chronic renal insufficiency
        - Causes in children
          - Structural (usually congenital)
          - Metabolic (oxalosis, cystinosis)
          - Acquired (infection)
        - The younger the age of onset, the greater the stature loss
        - Dialysis/transplant patients often do not normalize growth
      - Turner syndrome
      - Prader-Willi syndrome

#### Adult GH deficiency

- Epidemiology
  - Prevalence – uncommon
- Etiology

- Acquired pituitary damage – surgery, tumor, granulomas, cranial irradiation, trauma, hypophysitis
  - Usually a sequential loss in anterior pituitary function – loss of GH, follicle stimulating hormone and leuteinizing hormone (FSH and LH) may be followed by loss of thyroid stimulating hormone (TSH) and loss of adrenocorticotrophic hormone (ACTH)
- Acquired hypothalamic damage
- Pathophysiology
  - Almost always acquired damage to pituitary or, rarely, to hypothalamus
- Clinical Presentation
  - Constitutional – fatigue, low self-esteem
  - Increased body fat, reduced lean mass
  - Reduced exercise capacity
  - Dyslipidemia
  - Complications – coronary artery disease, hypertension, insulin resistance, osteopenia
- Treatment
  - GH replacement

## Diagnosis

### Childhood GH deficiency

- Indications for testing – severe short stature (>2 standard deviations below mean), severe growth deceleration, history of brain tumor, cranial irradiation, radiologic evidence of pituitary abnormality
- Diagnosis
  - Rule out all other causes of short stature first
    - Hypothyroidism
    - Chromosomal disorders
      - Prader-Willi syndrome
        - Genetic disorder involving deletion of long arm of chromosome 15
        - Incidence – 1/15,000
        - Infants – hypotonic with poor feeding
        - Age 2 – hyperphagic, short stature
        - Adults – prone to diabetes mellitus type 2, morbid obesity, hypogonadism
      - Turner syndrome
        - Chromosomal abnormality
        - Incidence – 1/2,000 live births
        - Short stature and infertility
      - Chronic systemic disease
        - Renal failure is most common
        - Malabsorption (celiac disease)
    - Skeletal disorders
    - ISS
  - Laboratory testing
    - GH levels alone cannot diagnose GH deficiency due to pulsatile nature of GH release
      - If GH levels after stimulation are low, then GH deficiency is confirmed; IGF-1 cannot be used as a single test to diagnose GH deficiency
    - Best test is insulin-induced hypoglycemia
      - Method – 0.1 unit of insulin/kg of body weight and measure GH at 0, 15, 30, 60 and 90 minutes

- GHRH plus arginine
- Other agents are L-dopa, arginine, clonidine and glucagon
- Normal stimulation result is GH >10 ng/mL in children, >5 ng/mL in adults
  - For children, some experts consider values of 7-10 ng/mL equivocal; >10 ng/mL is still considered normal
- Results suggestive of GH deficiency following stimulation tests
  - IGF-1 measurement low
  - IGFBP-3 measurement low

### Adult GH deficiency

- Indications for testing – evidence of hypothalamic-pituitary disease (GH deficiency in childhood, signs and symptoms of pituitary dysfunction in adulthood)
- Diagnosis
  - Laboratory testing
    - Diagnosis usually requires 2 positive stimulation tests
      - GH stimulation – insulin-induced hypoglycemia (ITT) or GHRH plus arginine stimulation recommended tests for adults
        - GHRH and GHRP-6 also available; arginine or glucagon stimulation alone might be alternatives
        - All tests affected by obesity
      - Arginine stimulation test
        - 0.5 g/kg body weight IV given over 30 minutes with serum GH at 0, 30, 60, 90 minutes; positive test is GH <3 ng/mL and hypoglycemia
        - This test is not as accurate as ITT in adults
        - Not affected by age
    - Results suggestive of GH deficiency following stimulation tests – IGF-1 (low), IGFBP-3 (low)
      - Severely low levels of IGF-1 can be used as evidence for GH deficiency
    - 3 or more pituitary hormone deficiencies occur with a low IGF-1
      - Consider testing other anterior pituitary hormones (LH/FSH, TSH, ACTH)
  - Imaging studies
    - If no obvious etiology of deficiency, perform CT or MRI to rule out tumor

### Monitoring

- Linear height velocity usually accelerates with GH replacement
  - May not occur in ISS
- Repeat GH testing – only necessary after puberty to assess if lifelong GH supplementation is necessary

## Lab Tests

### Indications for Laboratory Testing

Tests generally appear in the order most useful for common clinical situations. For test-specific information, refer to the test number in the ARUP Laboratory Test Directory on the ARUP Web site at [www.aruplab.com](http://www.aruplab.com).

Test Name and Number	Recommended Use	Limitations	Follow Up
Growth Hormone 0070080 Method: Chemiluminescent Immunoassay	Determine level of GH in a timed sample	Low or normal levels do not rule out GH deficiency	
IGF-1 (Insulin-Like Growth Factor I) 0070125 Method: Chemiluminescent Immunoassay	Use in assessment of GH deficiency	Increased in pubertal and pregnant patients Normal value does not rule out GH deficiency	May be used in conjunction with IGFBP-3
IGF Binding Protein-3 0070060 Method: Chemiluminescent Immunoassay	Use in assessment of GH deficiency	Normal value does not rule out GH deficiency	May be used in conjunction with IGF-1
Growth Hormone, 0 Minutes 0070081 Method: Chemiluminescent Immunoassay	Use in GH stimulation testing		
Growth Hormone, 30 Minutes 0070082 Method: Chemiluminescent Immunoassay	Use in GH stimulation testing		
Growth Hormone, 60 Minutes 0070083 Method: Chemiluminescent Immunoassay	Use in GH stimulation testing		

Growth Hormone, 90 Minutes <b>0070084</b> Method: Chemiluminescent Immunoassay	Use in GH stimulation testing		
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**Additional Tests Available**

Test Name and Number	Comments
IGF Binding Protein 2 <b>0098842</b> Method: Radioimmunoassay	
IGF Binding Protein-1 <b>0098843</b> Method: Radioimmunoassay	
Growth Hormone Antibody <b>0092142</b> Method: Radiobinding Assay	
Growth Hormone, 15 Minutes <b>0070048</b> Method: Chemiluminescent Immunoassay	
Growth Hormone, 45 Minutes <b>0070049</b> Method: Chemiluminescent Immunoassay	
Growth Hormone, 120 Minutes <b>0070164</b> Method: Chemiluminescent Immunoassay	
Insulin, 30 Minutes <b>0070064</b> Method: Chemiluminescent Immunoassay	
Insulin, 60 Minutes <b>0070066</b> Method: Chemiluminescent Immunoassay	
Insulin, 120 Minutes <b>0070068</b> Method: Chemiluminescent Immunoassay	

Luteinizing Hormone and Follicle Stimulating Hormone <b>0070193</b> Method: Electrochemiluminescent Immunoassay	
Thyroid Stimulating Hormone <b>0070145</b> Method: Electrochemiluminescent Immunoassay	
Adrenocorticotropic Hormone <b>0070010</b> Method: Chemiluminescent Immunoassay	

**Guidelines**

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