Diagnosing and Treating Patients for Adult Growth Hormone Deficiency
What should prompt a clinician to consider a diagnosis of adult GHD?
Manifestations of Adult GHD

- Fatigue, lack of energy
- Depressed mood, lack of interest in usual activities
- Decreased muscle strength and exercise capacity
- Decreased lean body mass
- Increased fat mass, weight gain
Consequences and Comorbidities Of Adult GHD

- Dyslipidemia
- Cardiac dysfunction
- Decreased fibrinolysis
- Premature atherosclerosis
- Decreased bone mineral density
- Increased insulin resistance
- Impaired quality of life

Adult GHD is Rare

- Adult-onset GHD is estimated to affect 1 per 100,000 people annually.

- Adult GHD can be caused by damage to the hypothalamic-pituitary region, often related to traumatic brain injury, pituitary tumors, or radiotherapy and surgery.

Gabreanu GR. Discoveries 2018, January-March; 6(1); e82.
Who Should Be Evaluated and Tested?

- The presenting symptoms and signs of adult GHD are typically non-specific. Symptoms alone cannot identify at-risk patients.

- There is no biological marker, such as the growth failure seen with child-onset GHD, and no pathognomonic feature of this disease.

- Therefore, clinicians should perform a comprehensive evaluation only on patients with a reasonable probability of GHD. These include patients with conditions known to cause adult GHD.

Gabreanu GR. Discoveries 2018, January-March; 6(1); e82.
## Causes of Adult GHD

Consider testing patients with these conditions

<table>
<thead>
<tr>
<th>Acquired</th>
<th>Congenital</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Skull-based lesions</strong></td>
<td><strong>Genetic</strong></td>
</tr>
<tr>
<td>Pituitary adenoma, craniopharyngioma, Rathke’s cleft cyst, meningioma, glioma/astrocytoma, hamartoma, chordoma, lymphoma, metastases</td>
<td>Transcription factor defects (PIT-1, PROP-1, LHX3/4, HESX-1, PITX-2)</td>
</tr>
<tr>
<td><strong>Brain injury</strong></td>
<td>GHRH receptor gene defects</td>
</tr>
<tr>
<td>TBI, sports-related head trauma, blast injury, perinatal insults</td>
<td>GH gene defects</td>
</tr>
<tr>
<td><strong>Infiltrative/granulomatous disease</strong></td>
<td>GH receptor/post-receptor defects</td>
</tr>
<tr>
<td>Langerhans cell histiocytosis, autoimmune hypophysitis, sarcoidosis, TB, amyloidosis</td>
<td>Associated with brain structural defects</td>
</tr>
<tr>
<td><strong>Surgery to sella, suprasellar and parasellar region</strong></td>
<td>Single central incisor</td>
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<tr>
<td><strong>Cranial irradiation</strong></td>
<td>Cleft lip/palate</td>
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<tr>
<td><strong>CNS infections</strong></td>
<td></td>
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<tr>
<td>Bacterial, viral, fungal, parasital</td>
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<tr>
<td><strong>Infarction/hemorrhage</strong></td>
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<tr>
<td>Apoplexy, Sheehan’s syndrome, SAH, stroke, snake bite</td>
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<tr>
<td><strong>Empty sella</strong></td>
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<tr>
<td><strong>Hydrocephalus</strong></td>
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</tbody>
</table>

Laboratory measurements such as IGF-1 or a single growth hormone measurement have poor diagnostic value because of the overlap with healthy adults, particularly those older than 40.

A GH stimulation test, therefore, is typically required to establish the diagnosis.
GH-stimulation testing is not required in certain patients who meet criteria that predict adult GHD with high specificity.

- Multiple pituitary hormone deficiency, defined as ≥3 pituitary hormone deficits and low serum IGF-1 levels (<–2.0 SDS), or organic hypothalamic-pituitary disease (for example, suprasellar mass with previous surgery and cranial irradiation).
- Genetic defects affecting the hypothalamic-pituitary axis, such as PIT-1, PROP-1, LHX3/4, HESX-1, and PITX-2 transcription factor defects
- Hypothalamic-pituitary structural brain defects
Patients with Fewer Pituitary Hormone Deficits

• In patients with ≤2 pituitary hormonal deficiencies (PHD), low-serum IGF-1 levels (≤-2.0 SDS) alone are not sufficient to make a diagnosis of adult GHD.

• In these patients, clinicians should perform one GH-stimulation test to confirm the diagnosis.
AACE 2019 CPG Algorithm for Testing Adult Patients with Clinical Suspicion of GHD

Adult patient with clinical suspicion of GHD

Organic GHD
≥3 hormone deficiencies
Low IGF-I (<−2.0 SDS)
No further testing required
Treat

Organic GHD
0, 1 or 2 hormone deficiencies
Low IGF-I (<0 SDS)
Further testing required

History of hypothalamic-pituitary tumors, surgery, cranial irradiation, empty sella, pituitary apoplexy, traumatic brain injury, subarachnoid hemorrhage, autoimmune hypophysitis or Rathke’s cleft cyst

High suspicion
Low IGF-I (<0 SDS)
Further testing required

Low suspicion
Normal IGF-I (≥0 SDS)
Observe

Legend for Glucagon Stimulation Test (GST)
Treat if:
- peak GH ≤ 3.0 µg/L in normal-weight (BMI < 25 kg/m²) patients
- peak GH ≤ 3.0 µg/L in overweight (BMI 25-30 kg/m²) patients with a high pre-test probability
- peak GH ≤ 1.0 µg/L in overweight (BMI 25-30 kg/m²) patients with a low pre-test probability
- peak GH ≤ 1.0 µg/L in obese (BMI > 30 kg/m²) patients

Diagnosis

Before GH Testing: Address Other Pituitary Hormone Deficits

- GH–stimulation tests should only be conducted after all the other pituitary hormone deficits have been optimally replaced with stable hormone-replacement doses.
- Over- or under-replacement of the other endocrine axes can potentially affect the results of GH testing.

Should primary care physicians refer to an endocrinologist?

Given the complexity of GHD and its possible association with other underlying pituitary deficiencies, patients with adult GHD or suspicion of this disease are best co-managed in partnership with an endocrinologist.
Diagnostic Tests
The Insulin Tolerance Test (ITT): Gold Standard

- Establishes a diagnosis of adult GHD, using a peak GH cut-point of 5 mg/L.

- Disadvantages:
  - It requires close medical supervision by a physician.
  - It may be unpleasant for patients as it can cause severe hypoglycemia.
  - It has potentially serious adverse effects (including seizures and altered consciousness resulting from neuroglycopenia).

- Contraindicated in the elderly and in patients with a history of cardiovascular and cerebrovascular disease and seizures.

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Alternatives to the Insulin Tolerance Test

- Because of the practicalities of performing the ITT, it has been used less frequently in the United States in recent years.

- If the ITT is contraindicated or is not feasible, the glucagon-stimulation test (GST) and/or the macimorelin test can be considered as alternatives.
# Comparison of the Glucagon Stimulation and Macimorelin Tests

Other agents such as arginine and L-Dopa are weak GH stimulants and should not be used in adults

<table>
<thead>
<tr>
<th>Testing</th>
<th>Advantages</th>
<th>Disadvantages</th>
<th>Side Effects</th>
<th>Cut Points</th>
</tr>
</thead>
</table>
| **Glucagon Stimulation Test** | • Reproducible  
• Safe  
• Not influenced by sex or hypothalamic origin of disease | • Long duration: 3-4 hours  
• Requires multiple blood draws  
• Intramuscular injection | • Nausea, vomiting, headache  
• Usually resolve within 4 hours | 3 µg/L: normal weight pts. and overweight pts. with high pretest possibility  
1 µg/L : obese pts. and overweight pts. with low pretest possibility |
| **Macimorelin Test** | • Oral admin  
• No hypoglycemia  
• Short (90 min), with only 4 sample collections required | Cost: one 60 mg packet costs approximately $4,500 | Mild dysgeusia reported most commonly, which did not require intervention and resolved spontaneously | 2.8 mg/L  
Not yet known whether adjusted cut-points are needed for overweight and obese patients |

Physical Exam and Laboratory Tests to Follow in Patients Receiving GH Replacement Therapy
Adult Growth Hormone Replacement

- In the United States rhGH (somatropin) is approved by the FDA for adult GHD and marketed under various trade names.
- There is no evidence that one product is different or more advantageous than another, apart from differences in pen devices, electronic auto-injector devices that are user-friendly, dose adjustments, and refrigeration requirements.
- Benign intracranial hypertension presenting with papilledema and headaches has been reported in children on rhGH therapy, and rarely in adults. The FDA recommends an eye exam to exclude pre-existing papilledema before initiating certain products. Check the prescribing information of the product you use.

Goals of Treatment

• Aim to increase serum IGF-1 levels to reach between age-adjusted IGF-1 SDS –2 and +2, unless side effects occur.

• An age-adjusted IGF-1 SDS of 0 is ideal.

• If patient is doing well and IGF-1 SDS <2, consider a trial of higher dose of rhGH.

Once stable rhGH doses are maintained, clinicians should monitor the following parameters at approximately 6- to 12-month intervals:

- Serum IGF-1
- Fasting glucose
- Hemoglobin A1c
- Fasting lipids
- BMI
- Waist circumference
- Waist-to-hip ratio
- Serum-free T4
In patients not on glucocorticoid replacement, the hypothalamic-pituitary-adrenal axis should be assessed via early morning cortisol or cosyntropin-stimulation test if symptoms suggestive of adrenal insufficiency are experienced, particularly after a dose increase of rhGH.

Patients on glucocorticoid replacement may need dose increments after starting GH replacement therapy and should be monitored for new deficiencies.
Quality of Life

• Adults with GHD have diminished quality-of-life.

• Evaluation of overall clinical status including assessment of QOL using the Quality of Life Assessment of Growth Hormone Deficiency in Adults (QoL-AGHDA) questionnaire at 12-month intervals is suggested.

Adults with GHD have an increased risk of cardiovascular morbidity and mortality. Cardiovascular parameters to consider monitoring during follow-up include:

- Systolic and diastolic blood pressure
- Heart rate
- Electrocardiogram, echocardiogram, and carotid echo-Doppler examinations may be performed if clinically indicated according to local best clinical practice.

Bone Health

- Measurements of bone mineral content and BMD should be taken before starting rhGH therapy.

- If the initial bone DXA scan is abnormal, bone DXA scans should be repeated at 2- to 3-year intervals to assess the need for additional bone treatment modalities.
In patients with significant residual tumor in the hypothalamic-pituitary region, baseline and periodic MRI scans should be undertaken before and during rhGH therapy to monitor the size of the pituitary lesion or any changes in post-surgical residual tumor.

Levothyroxine Replacement

- Patients on concurrent levothyroxine replacement may need dose increments after starting GH replacement therapy.

- Patients not already on levothyroxine should be monitored for the possibility of deficiencies, with replacement given if needed.
How long should growth hormone replacement be continued?

- The appropriate length of rhGH therapy is unclear. If benefits are achieved, treatment can be continued indefinitely.

- If no apparent or objective benefits are achieved after at least 12-18 months, discontinuing therapy may be considered.

- If patients decide to discontinue, a 6-month follow-up appointment is recommended, because some patients may want to resume therapy, realizing in retrospect they felt better on treatment.

Long-Term Monitoring

- After more than 20 years of adult rhGH replacement, there are no data to suggest it increases cancer risk or accelerates recurrences of tumors in the hypothalamic-pituitary region.

- Long-term monitoring and cancer screening should be exactly the same in GH-treated patients as in normal patients.

Long-Term Data

3,180 adults treated with GH replacement in two multicenter studies, followed for up to 12 years

Safety data based on physician reporting of adverse events.

No new safety signals observed.
References:


• Melmed S “Pathogenesis and Diagnosis of Growth Hormone Deficiency in Adults” *NEJM* 2019;380(26):2551-62.


• Gabreanu GR “An update on the diagnosis of growth hormone deficiency” *Discoveries* 2018, January-March; 6(1); e82. DOI:10.15190/d.2018.2


Thank You

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