DOES GH KEEP YOU YOUNGER?

Shlomo Melmed, MD
AACE Meeting
May 2016

Hypothalamic releasing and inhibiting hormones
Superior hypophysial artery

IGF-I
SRF
GHRH

GH

Melmed NEJM 2006

Levin D, J NHP Rev 1995
GH/IGF1 action

![Graph showing body weight (g) over time with markers for IGFI, GH, and NaCl.]

Guler, Nature, 1986

GH – IGF-1 System

![Diagram illustrating somatic mass and age with symmetrical mature adult and sarcopenia stages.]

Symmetrical mature adult

sarcopenia

Differentiation

Growth

Homeostasis

Maintenance

Age

Somatic Mass
Causes of Acquired GHD

**Trauma**
- CNS infection
- Radiation
- CVA
- Surgery

**Tumors**
- Pituitary adenoma
- Craniopharyngioma
- Rathke’s cleft cyst
- Glioma
- Metastatic

**Infiltrative/granulomatous disease**
- Histiocytosis
- Sarcoidosis
- Tuberculosis
- Hypophysitis

**Cryptic**
- Transcription factor antibodies
- Subtle structural changes

Who should get tested for acquired AGHD?

Testing for adult GHD should only be undertaken in patients with suspected hypothalamic-pituitary disorders.

1. Appropriately **blunted GH** response to provocative test.

2. **Low IGF-I** increases likelihood of diagnosis, and may distinguish obesity.
Adult GH Secretion Following ITT (0.1 U/kg)

<table>
<thead>
<tr>
<th>GH (µg/L)</th>
<th>29 Hypopituitary Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 2</td>
<td>17</td>
</tr>
<tr>
<td>&lt; 5</td>
<td>25</td>
</tr>
<tr>
<td>&lt; 7.5</td>
<td>28</td>
</tr>
<tr>
<td>&lt; 23</td>
<td>29</td>
</tr>
<tr>
<td>Normal (6)</td>
<td>36 ±21</td>
</tr>
</tbody>
</table>

Landon, J Clin Invest, 1966

Adult GH Deficiency

<table>
<thead>
<tr>
<th>ITT</th>
<th>GHD</th>
<th>Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean 24 h GH (q20 min)</td>
<td>0.2 ± 0.1</td>
<td>0.7 ± 0.1</td>
</tr>
<tr>
<td>Mean 24 h GH &lt; 0.2</td>
<td>74%</td>
<td>15%</td>
</tr>
<tr>
<td>IGF-I</td>
<td>0.4 ± 0.1</td>
<td>0.7 ± 0.1</td>
</tr>
</tbody>
</table>

Hoffman, Lancet, 1994
Mildly Elevated BMI Blunts Evoked GH in Healthy Adults

![Graph showing GH peak (ng/ml) vs BMI](image)

Challenges to diagnosis

Abdominal obesity
BMI
Age
Gender
Assay rigor
## Diagnosis of AGHD

<table>
<thead>
<tr>
<th>Clinical</th>
<th>Imaging</th>
<th>Lab</th>
</tr>
</thead>
<tbody>
<tr>
<td>History of pituitary damage</td>
<td>Decreased bone density</td>
<td>Evoked GH &lt; 3</td>
</tr>
<tr>
<td>Truncal obesity</td>
<td>Excess omental adiposity</td>
<td>IGF-I and IGFBP3 low or normal</td>
</tr>
<tr>
<td>Psychosocial impairment</td>
<td></td>
<td>Hypercholesterolemia, low HDL, high LDL</td>
</tr>
</tbody>
</table>

### Adult GH Deficiency

<table>
<thead>
<tr>
<th>IMPAIRED QUALITY OF LIFE</th>
<th>CARDIOVASCULAR RISK FACTORS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased energy and drive</td>
<td>Abnormal cardiac structure and function</td>
</tr>
<tr>
<td>Poor concentration</td>
<td>Abnormal lipids</td>
</tr>
<tr>
<td>Low-self esteem</td>
<td>Decreased fibrinolysis</td>
</tr>
<tr>
<td>Social isolation</td>
<td>Atherosclerosis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>REDUCED EXERCISE CAPACITY</th>
<th>REDUCED BONE DENSITY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduced max O₂ uptake</td>
<td></td>
</tr>
<tr>
<td>Impaired cardiac function</td>
<td></td>
</tr>
<tr>
<td>Reduced muscle mass</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>ABNORMAL BODY COMPOSITION</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased fat mass</td>
<td></td>
</tr>
<tr>
<td>Altered fat distribution</td>
<td></td>
</tr>
<tr>
<td>Decreased lean body mass</td>
<td></td>
</tr>
</tbody>
</table>
**GH action in AGHD**

**Lean Body Mass (kg)**
- GH: Blue line with square markers
- Placebo: Red line with square markers

**Fat Mass (kg)**
- GH: Blue line with square markers
- Placebo: Red line with square markers

*Months*

Cunéo, NEJM, 1989

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**GH action in AGHD**

**Serum Igf-I**
- GH, men + women
- GH, men
- GH, women
- Placebo, (men + women)

**Body weight**
- GH, men + women
- GH, men
- GH, women
- Placebo, (men + women)

**Fat free mass**
- GH, men + women
- GH, men
- GH, women
- Placebo, (men + women)

**Body fat**
- GH, men + women
- GH, men
- GH, women
- Placebo, (men + women)

Ehrnborg, Clin Endocrinology, 2005
## Meta-analysis of GH Effects on Cardiovascular Risk Factors

![Global effect (95% CI)](image)

- Lean body mass
- Fat mass
- LDL Chol.
- D.BP
- S.BP
- Insulin
- Glucose

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## Adult GH Deficiency

Ten-Year Change in Quality of Life in Adults on Growth Hormone Replacement for Growth Hormone Deficiency: An Analysis of the Hypopituitary Control and Complications Study

Daqun Mo, Werner F. Blum, Myriam Rosilio, Susan M. Webb, Rong Qi, Christian J. Strasburger

Predictors for change in QLS-H Z-score in GH-treated GHD

<table>
<thead>
<tr>
<th>Categorical Variable Level</th>
<th>Parameter Estimate (Slope)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depression</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>0.271</td>
<td>.0059</td>
</tr>
<tr>
<td>Yes</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

Body mass index

| QLS-H Z-score at entry | -0.025 | <.001 |

GH causes sustained QLS-H score improvement in 1532 patients for 10 yrs

Mo, J Clin Endocrinol Metab, 2014
Adult GH Replacement

Exclude contra-indications
- No active tumor
- No retinopathy
- Diabetes controlled

Pituitary pathology
Clinical features
Evoked GH <3μg/L
IGF-I maybe low

GH replacement

Measure IGF-I after 1 month

Titrte GH dose to normalize IGF-I to age-and gender-matched controls, or until symptom tolerance

No clinical response after 6 months
Discontinue Rx

Clinical response
Continue treatment
Monitor IGF-I, lipids; bone density

Unique dose requirements:
Women on estrogen;
elderly patients

GH Replacement Reverses Body Composition Changes

- Lean body mass increased
- Fat mass decreased
- Waist-to-hip ratio reverts
- Muscle mass increases
Somatopause

GHRH

DECREASED

GH

IGF-I

Synthesis
Secretion
Receptors

Synthesis
Secretion
Half-life
Binding-proteins

Levels
Responses to GH
BP-3

Abrogated GH signaling increases life span

GH Signals

Growth
IGF-I ↓
mTOR ↓
Body size ↓
Cancer ↓

Defense Mechanisms
Stress resistance ↑
Xenobiotic metabolism ↑
Oxidative damage ↓

Inflammation
Adiponectin ↑
IL-6 ↓
TNFα ↓

Metabolic
F.A.oxidation ↑
Insulin sensitivity ↑

Healthspan and Lifespan

Bartke, Physiol Rev 2013
GH/IGF 1 regulates NLRP3 inflammasome

- Long-lived GH/IGF-I mutants protected from *inflammaging*
- IGFIR ablation inhibits inflammasome

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Longevity increased in mutant dwarf mice

- Graph showing increased longevity in GHD mutant dwarf mice compared to WT

Brown-Borg, Nature 1996
**Overexpressed GH reduces survival**

![Graph showing cumulative survival over days alive, with data from Bartke, Neuroendocrinology, 2003](image)

**GH deficiency protects against cancer**

![Pie charts comparing relatives and GHRD, with data from Guevara-Aguirre, Sci Trans Med, 2011](image)
Age-distribution for 90 living GHRD subjects and Controls

Evidence against GH as anti-aging Rx

- GHD mouse models are long-lived
- GH/IGF I role in cancer
- Insulin resistance development
- GH/IGF I induce inflammaging
The Elderly Obtain ‘Rejuvenation’ Drug

Providing Growth Hormone Is Just the Latest Venture of a Fertile Entrepreneur

THE WALL STREET JOURNAL  JANUARY 10, 1996

Grey Market

Rx GH in Elderly

- Improved body composition
- No functional improvement
- No gain in muscle strength or power
- No improved muscle endurance or aerobic capacity

GH replacement benefits known hypothalamic-pituitary disease

No proven GH benefit in ‘somatopause’

Athletic GH doping is illegal, and has no scientific or ethical justification.

Clemmons, JCEM, 2014
Average muscle strength to progressive resistant exercise

![Graph showing muscle strength progress over weeks for Placebo and GH .02 μg/kg/day.](image)

Liu, Bravata, Olkin, Nayak, Roberts, Garber, and Hoffman

**Conclusions:** Literature on randomized, controlled trials evaluating GH therapy in healthy elderly is limited but suggests that it is associated with *small changes in body composition* and *increased adverse events*. On the basis of this evidence, GH cannot be recommended as an antiaging therapy.


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Systematic Review: Safety and Efficacy of Growth Hormone in the Healthy Elderly
Liu, Bravata, Olkin, Nayak, Roberts, Garber, and Hoffman

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Annals of Internal Medicine

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5/19/2016
GH as a Mortality Determinant: The Golden Window

Mortality

GHD

Acromegaly

control

GH
Effects of GH on Adipose Tissue

- Adipocyte size ↓
- Lipolysis ↑
- Lipogenesis ↓

Somatotropin Replacement Skinfold Response

GH Causes Regional Fat Loss

Bengtsson, JCEM, 1993