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Adult Growth Hormone Deficiency:
An Introduction to the New 2019 Guidelines

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Acknowledgments

2019 AACE GROWTH HORMONE TASK FORCE MEMBERS

Kevin C.J. Yuen (chair), Beverly M. K. Biller, Sally Radovick, John D. Carmichael, Sina Jasim, Kevin M. Pantalone, and Andrew R. Hoffman

Disclosures

- Received research grants as Principal Investigator to Barrow Neurological Institute from Pfizer, Novo Nordisk, and Aeterna Zentaris
- Served as an occasional consultant for Pfizer, Novo Nordisk, Sandoz, Aeterna Zentaris, and Strongbridge
2009 AACE guidelines for adults and transition patients with GH deficiency
So why update the 2009 guidelines?

- More evidence of beneficial effects of GH replacement
- Still some skepticism in the US about GH:
  - high cost of therapy and its true benefits
  - need to administer daily injections
  - difficulty conducting GH stimulation tests in the office
  - concerns about safety of long-term therapy
  - inappropriate GH dosing in certain types of patients
  - still a misconception of true adult GHD vs physiological decline in GH secretion due to aging
  - increasing GH use in non-medical conditions
- Recent years, several sub-populations of patients described to be “at risk” for adult GHD
  - how to reliably test?
  - when and how to treat?
- New developments
Outline of the new 2019 guidelines

1. What is adult GHD and why treat?
2. Are there any differences between CO-GHD vs AO-GHD?
3. How should CO-GHD patients be transitioned to adult care services?
4. What are the benefits of continuing GH replacement in transition patients?
5. Who should be tested?
6. How should one test for adult GHD?
7. Why are standardized GH and IGF-I assays important in the management of adult GHD?
8. How should initiation and monitoring of GH replacement be done?
9. Can GH be used during conception and pregnancy?
10. What are the side-effects of GH replacement?
11. How safe is long-term GH replacement therapy?
12. Can GH be used for sports and aging?
13. What are the recent developments in this field?
What is adult GHD?
Clinical features of adult GHD

- Decreased lean body mass
- Bone mineral density
- Physical performance
- Cardiac capacity
- Central fat deposition
- Glucose intolerance
- Dyslipidemia
- Intima-media thickness
- Psychosocial issues
  - Low self-esteem
  - Depression
  - Mental fatigue
  - Poor memory
  - Impaired cognition
  - Social isolation
  - Dissatisfaction with body image

### Conditions and treatment that can cause adult GHD

<table>
<thead>
<tr>
<th>Acquired</th>
<th>Congenital</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Skull base lesions</strong></td>
<td><strong>Genetic</strong></td>
</tr>
<tr>
<td>Pituitary adenoma, craniopharyngioma, Rathke’s cleft cyst, meningioma,</td>
<td>Transcription factor defects (PIT-1, PROP-1, LHX3/4,</td>
</tr>
<tr>
<td>glioma/astrocytoma, hamartoma, chordoma, lymphoma, metastases</td>
<td>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></td>
<td>GH receptor/post-receptor defects</td>
</tr>
<tr>
<td><strong>Infiltrative/granulomatous disease</strong></td>
<td><strong>Associated with brain structural defects</strong></td>
</tr>
<tr>
<td>Langerhans cell histiocytosis, autoimmune hypophysitis, sarcoidosis, TB,</td>
<td>Single central incisor</td>
</tr>
<tr>
<td>amyloidosis</td>
<td>Cleft lip/palate</td>
</tr>
<tr>
<td><strong>Surgery to the sella, suprasellar and parasellar region</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Cranial irradiation</strong></td>
<td></td>
</tr>
<tr>
<td><strong>CNS infections</strong></td>
<td></td>
</tr>
<tr>
<td>Bacterial, viral, fungal, parasital</td>
<td></td>
</tr>
<tr>
<td><strong>Infarction/hemorrhage</strong></td>
<td></td>
</tr>
<tr>
<td>Apoplexy, Sheehan’s syndrome, SAH, stroke, snake bite</td>
<td></td>
</tr>
<tr>
<td>Empty sella</td>
<td></td>
</tr>
<tr>
<td>Hydrocephalus</td>
<td></td>
</tr>
<tr>
<td>Idiopathic</td>
<td></td>
</tr>
</tbody>
</table>
Why treat adult GHD?
Effects of GH replacement in adults with GHD:

*body composition, lipids, BP and glucose*

A meta-analysis of blinded, randomized, placebo-controlled trials

<table>
<thead>
<tr>
<th>Factors</th>
<th>No. of trials</th>
<th>Treatment</th>
<th>Q test</th>
<th>Weighted mean (sd) change (GH-placebo)</th>
<th>Global effect size (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lean B mass</td>
<td>19</td>
<td></td>
<td>ns</td>
<td>2.82 kg (2.68)</td>
<td></td>
</tr>
<tr>
<td>Fat mass</td>
<td>13</td>
<td></td>
<td>ns</td>
<td>-3.05 kg (3.29)</td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td>8</td>
<td></td>
<td>ns</td>
<td>-0.12 kg/m² (1.40)</td>
<td></td>
</tr>
<tr>
<td>TG</td>
<td>11</td>
<td></td>
<td>ns</td>
<td>0.07 mmol/liter (0.36)</td>
<td></td>
</tr>
<tr>
<td>HDL Chol.</td>
<td>13</td>
<td></td>
<td>ns</td>
<td>0.06 mmol/liter (0.09)</td>
<td></td>
</tr>
<tr>
<td>LDL Chol.</td>
<td>13</td>
<td></td>
<td>ns</td>
<td>-0.53 mmol/liter (0.29)</td>
<td></td>
</tr>
<tr>
<td>Total Chol.</td>
<td>15</td>
<td></td>
<td>ns</td>
<td>-0.34 mmol/liter (0.31)</td>
<td></td>
</tr>
<tr>
<td>D.B.P.</td>
<td>10</td>
<td></td>
<td>ns</td>
<td>-1.80 mm Hg (3.77)</td>
<td></td>
</tr>
<tr>
<td>S.B.P.</td>
<td>9</td>
<td></td>
<td>ns</td>
<td>2.06 mm Hg (5.34)</td>
<td></td>
</tr>
<tr>
<td>Insulin</td>
<td>11</td>
<td></td>
<td>ns</td>
<td>8.66 pmol/liter (6.98)</td>
<td></td>
</tr>
<tr>
<td>Glucose</td>
<td>13</td>
<td></td>
<td>ns</td>
<td>0.22 mmol/liter (0.14)</td>
<td></td>
</tr>
</tbody>
</table>

Lean B mass, Lean body mass; TG, triglycerides; Chol., cholesterol; D.B.P., diastolic blood pressure; S.B.P., systolic blood pressure; ns, nonsignificant.

Effects of GH replacement in adults with GHD: bone mineral density

Effects of GH replacement in adults with GHD: exercise capacity

Effects of GH replacement in adults with GHD: *QoL and sick day leave*

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>Sick leave (days/6 months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>12.2 ± 3.9</td>
</tr>
<tr>
<td>6</td>
<td>7.2 ± 3.5</td>
</tr>
<tr>
<td>12</td>
<td>2.9 ± 1.6</td>
</tr>
<tr>
<td>18</td>
<td>0.4 ± 0.2</td>
</tr>
<tr>
<td>24</td>
<td>3.3 ± 2.5</td>
</tr>
</tbody>
</table>


Effects of GH replacement in adults with GHD: *partner’s response to health questionnaire*

<table>
<thead>
<tr>
<th>Item</th>
<th>Placebo (%)</th>
<th>GH (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>a More alert</td>
<td>0.0</td>
<td>69.0</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>b More active</td>
<td>3.7</td>
<td>51.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>c Higher endurance</td>
<td>3.6</td>
<td>60.7</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>d Less easily annoyed</td>
<td>7.1</td>
<td>28.6</td>
<td>&lt;0.10</td>
</tr>
<tr>
<td>e Less worried</td>
<td>6.9</td>
<td>37.9</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>f More extrovert</td>
<td>3.4</td>
<td>37.9</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>g More industrious</td>
<td>3.3</td>
<td>46.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>h More happy</td>
<td>11.1</td>
<td>48.1</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>i Better looks</td>
<td>10.3</td>
<td>51.7</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>j More satisfied with his/her occupation</td>
<td>7.7</td>
<td>34.6</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>k Fewer family conflicts</td>
<td>3.4</td>
<td>24.1</td>
<td>&lt;0.10</td>
</tr>
<tr>
<td>l Better personal relationships</td>
<td>3.4</td>
<td>34.5</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>
Potential impact of untreated GHD vs GH replacement on cardiovascular risk

UNTREATED ADULT GHD REPLACEMENT

CV RISK FACTORS

CONVENTIONAL
- Lipids (total cholesterol, LDL, TG) ↑
- Glucose intolerance/hyperglycemia ↑
- β-cell function ↓
- Insulin resistance ↑
- Metabolic syndrome ↑

SURROGATE CV RISK MARKERS
- CRP ↑
- Pro-inflammatory cytokines (IL-6, TNF-α) ↑
- Adipokines (adiponectin ↑, leptin ↑/↓)
- Pregnancy-associated plasma protein A ↑
- Coagulation system (pro-coagulation ↑)
- Endothelial dysfunction ↑

INCREASED INDIVIDUAL CV RISK IMPROVED
Life expectancy in adults with NFPA receiving GH replacement therapy

How to test for adult GHD?
Pulsatile pattern of 24-hr GH secretion in a 30 y/o vs 60 y/o healthy adult vs an adult with GHD
Serum IGF-I levels throughout life

Men (n = 81)

Women (n = 71)

Normal range

IGF-I more reliable for screening for diagnosis in young adults

Examples of low IGF-I that may not be caused by GHD

- Malnutrition
- Poorly controlled diabetes
- Untreated hypothyroidism
- Kidney failure
- Liver disease
- Assay variability
Algorithm for testing transition patients with clinical suspicion of GHD

Transition patient with clinical suspicion of GHD

Congenital defects
- Genetic defects
- Organic disease
  - ≥ 3 hormone deficiencies
  - Low IGFI-I (<-2.0 SDS)

No further testing required
- Treat

Organic disease
- 0, 1 or 2 hormone deficiencies
- Low IGFI-I (< 0 SDS)

Further testing required

Organic disease
- Macimorelin
  - Peak GH ≤ 2.8 µg/L
  - Treat

Macimorelin
- Peak GH ≤ 5.0 µg/L
  - Treat

ITT
- Peak GH ≤ 5.0 µg/L
  - Treat

GST
- (see Legend)

Idiopathic isolated childhood GHD or suspected hypothalamic GHD

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

High suspicion
- Multiple hormone deficiencies
  - Low IGFI-I (< 0 SDS)
  - Further testing required

Low suspicion
- Further testing required

ITT
- Peak GH ≤ 5.0 µg/L
  - Treat

Macimorelin
- Peak GH ≤ 2.8 µg/L
  - Treat

Legend for GST
Treat if:
- peak GH ≤ 3.0 µg/L in patients with BMI < 25 kg/m²
- peak GH ≤ 1.0 µg/L in patients with BMI ≥ 25 kg/m²

GST
- (see Legend)
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

Macimorelin
Peak GH ≤ 2.8 μg/L
Treat

ITT
Peak GH ≤ 5.0 μg/L
Treat

GST
(see Legend)

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

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

High suspicion
Multiple hormone deficiencies
Low IGF-I (≤ 0 SDS)

Further testing required

Macimorelin
Peak GH ≤ 2.8 μg/L
Treat

ITT
Peak GH ≤ 5.0 μg/L
Treat

GST
(see Legend)

Legend for GST
Treat if:
- peak GH ≤ 3.0 μg/L in patients with BMI < 25 kg/m²
- peak GH ≤ 1.0 μg/L in patients with BMI ≥ 25 kg/m²
Presence of adult GHD is related to severity of hypopituitarism


≥3 deficiencies with low IGF-I sufficient to make the diagnosis
Lower GH cut-point recommended for the GST

ROC curve analysis to determine the cut-off peak GH response during the GST

Previous GST studies suggesting the effects of central adiposity and glucose intolerance in decreasing peak GH levels

- Wilson et al. *Growth Horm IGF Res* 2016 Feb;26:24-31
To reduce the possibility of over-diagnosing adult GHD in overweight/obese patients with the GST, a lower GH cut-point of 1 μg/L should be considered.
Oral Macimorelin GH test
Diagnostic accuracy comparable to the GHRH-arginine test for the diagnosis of adult GHD
Oral Macimorelin test
Validation Phase 3 study comparing with the ITT for the diagnosis of adult GHD

- Greater pituitary GH secretion than the ITT
- Sensitivity (87%) and specificity (96%) with cut-point of 2.8 μg/L vs ITT cutpoint of 5.1 μg/L
- Highly reproducible and good safety profile

Now approved in by the FDA and EMA
Estimated specificities and sensitivities of Macimorelin and ITT

How to transition patients?
Case 1: 17-year old female with idiopathic isolated GHD treated with GH since age 6

- Delayed bone age < 3rd percentile for age, and height and growth velocity < 3rd percentile
- Puberty at 12.5 years of age, but 8 months ago, growth velocity decreased to 3.5 cm/year
- MRI normal pituitary gland
- Currently:
  - GH dose: 0.033 mg/kg/day
  - height: 170 cm (mid-parental height: 175 cm)
  - growth velocity: 2.2 cm/year
  - body weight: 68 kg (BMI: 23 kg/m²)
  - bone age: 17 years

“I am tired of the shots”
Why is it so challenging to transition patients?

- Significant physiological changes occur during adolescence
- Young people may feel more comfortable with their ped endos
- Parental trust issues with adult endos
- Ped endos reluctant to “hand over” patients to adult endos
- Adult endos might think that ped endos “overprotective” and do not sufficiently prepare patients for the transition
Why is it so difficult to resume and maintain GH treatment in transition patients?

- “Injection fatigue”
- GH stimulation tests are difficult to perform
- Concerns about efficacy and AEs associated with continued treatment
- Young adults seek independence
- Cost of treatment and lack of medical insurance
- Lack the experience to coordinate their care
- Lack of understanding of metabolic consequences associated with discontinuing treatment
Bridging the gap: metabolic and endocrine care of patients during transition

Anita Hokken-Koelega1,*,†, Aart-Jan van der Lely1,*,†, Berthold Hauffa2,*,†, Gabriele Häusler3,†, Gudmundur Johannsson4,†, Mohamad Maghnie5,†, Jesús Argente6,*, Jean DeSchepper7,†, Helena Gleeson6,‡, John W Gregory6,‡, Charlotte Höybye8,‡, Fahrettin Keleştimur8,‡, Anton Luger9,‡, Hermann L Müller10,‡, Sarah-Kate Maguire11,‡, Yvon Nagao12,‡, Elke von Ruckmann13,‡, Lennart Edvardsson14,‡, Jean-François Dupont15,‡

“Even amongst healthcare professionals with an interest in improving transition services for patients with endocrine diseases, there is still much work to be done to improve the quality of healthcare for transition patients”
Recommendations for a successful transition process

- Coordinated approach between pediatric and adult endos
- Pediatrician to start educating patients early
- Develop a flexible plan tailored to the needs of each patient
- Assess independence and ability for self-care
- Provide assistance with reimbursement issues
- Patients who do not re-test as GH deficient should still continue to be monitored
Recommendations for continuing GH replacement in transition patients

• Close F/U during transition as untreated patients have lower BMD, more adverse body composition abnormalities and CV risk markers than AO-GHD

• Resuming GH replacement therapy in patients with confirmed persistent GHD during transition is recommended as most studies have demonstrated improved body composition, BMD, QoL and lipid profiles after 2 yrs of GH therapy vs those who did not receive GH therapy
Importance of peak bone mass in the development of osteoporosis

How to treat adult GHD?
Case 2: 26-year old woman with GHD due to NFA

<table>
<thead>
<tr>
<th>Status</th>
<th>GH dose/day</th>
<th>IGF-I (RR: 114-492)</th>
</tr>
</thead>
<tbody>
<tr>
<td>On OCP</td>
<td>2.0 mg</td>
<td>210 ng/mL</td>
</tr>
<tr>
<td>Stop OCP</td>
<td>2.0 mg</td>
<td>610 ng/mL</td>
</tr>
<tr>
<td>6 mths after stopping</td>
<td>1.0 mg</td>
<td>328 ng/mL</td>
</tr>
<tr>
<td>12 mths after stopping</td>
<td>0.8 mg</td>
<td>294 ng/mL</td>
</tr>
</tbody>
</table>
Women on oral estrogen require higher doses of GH to normalize their IGF-I levels

* $P < 0.05$ by ANOVA

How do we adjust the GH dose when patient is on oral estrogen and when oral estrogen is stopped?

General rule:

• Start or reduce the GH dose by ~ 50% for oral estrogen users
• Start or reduce the GH dose by ~ 30% in transdermal estrogen users
Case 3: 36-year old woman with Sheehan syndrome (1)

- Gestational diabetes 4 years ago
- Gradual weight gain
- Increasing fatigue and scanty menses
- Peak GH after ITT 1.8 ng/mL
- IGF-I 103 ng/mL (RR: 114-492 ng/mL)
### Case 3: 36-year old woman with Sheehan syndrome (2)

<table>
<thead>
<tr>
<th>Date</th>
<th>Weight (lbs)</th>
<th>Fasting glucose (mg/dL)</th>
<th>HbA1c (%)</th>
<th>IGF-I (ng/mL)</th>
<th>GH dose (mg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3/5/13</td>
<td>337</td>
<td>112</td>
<td>5.3</td>
<td>281</td>
<td>0.7</td>
</tr>
<tr>
<td>7/2/13</td>
<td>339</td>
<td>131</td>
<td>5.5</td>
<td>358</td>
<td>1.0</td>
</tr>
<tr>
<td>1/5/14</td>
<td>356</td>
<td>167</td>
<td>7.5</td>
<td>289</td>
<td>1.0</td>
</tr>
</tbody>
</table>
High GH dose (mean dose 6.7 µg/kg/day) impairs insulin sensitivity and postload glucose tolerance

- OGTT (mean + SEM)
- Top: Glucose v time
- Middle: Insulin v time
- Bottom: C-peptide v time

--- Before GH

---------- After GH

Effects of low dose GH therapy in adults with GHD: Insulin sensitivity (clamp studies)

Effects of low dose GH therapy in adults with GHD: Bioactive IGF-I

Recommendations for glucose control during GH therapy

- Encourage weight reduction
- Start with low GH doses initially
- GH dose reduction
- Anticipate glucose problems if patient is:
  - overweight/obese
  - previous Hx of gestational diabetes
- Adjust or add anti-diabetic medications
Case 4: 62-year old woman with hypopituitarism (1)

- TSS in 2016 for non-functioning macroadenoma
- On Levothyroxine 75 mcg/day and Hydrocortisone 10 mg/day
- Started on low dose GH therapy (0.2 mg/day) as fasting glucose levels were 115 mg/dL
- Since starting GH therapy, feeling more tired especially in the evenings
Case 4: 62-year old woman with hypopituitarism (2)

- Admitted to the ER with nausea, and lightheadedness
- AM cortisol 5.8 µg/dL and free T4 1.1 ng/dL
- Treated with IV fluids and IV Hydrocortisone
- Dose of Hydrocortisone increased to 20 mg daily (15/5) and Levothyroxine to 100 mcg/day, while GH dose kept at 0.3 mg/day
- Symptomatically much better
Cortisol metabolism regulated by $11\beta$HSD 1 and 2
GH inhibits 11βHSD1 activity at low doses in hypopituitary patients

Alteration in circulating thyroid hormones during GH replacement

<table>
<thead>
<tr>
<th></th>
<th>Pre-GH</th>
<th>Δ</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Free T4 (pmol/l)</td>
<td>12.9 ± 4.0</td>
<td>-1.09 ± 1.99*</td>
<td>0.02</td>
</tr>
<tr>
<td>Total T4 (nmol/l)</td>
<td>109 ± 4.9</td>
<td>-9.6 ± 4.25*</td>
<td>0.04</td>
</tr>
<tr>
<td>Free T3 (pmol/l)</td>
<td>5.4 ± 0.2</td>
<td>+0.34 ± 0.15*</td>
<td>0.03</td>
</tr>
<tr>
<td>Total T3 (nmol/l)</td>
<td>1.72 ± 0.4</td>
<td>-0.02 ± 0.32</td>
<td>0.76</td>
</tr>
<tr>
<td>RT3 (ng/dl)</td>
<td>17.6 ± 1.4</td>
<td>-3.44 ± 1.42*</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Glynn et al. *Clin Endocrinol (Oxf)* 2017 May;86(5):747-754

Behan et al. *Clin Endocrinol (Oxf)* 2011 Mar;74(3):281-288
Recommendations for starting GH doses in adults with GHD

- Age < 30 years: 0.4-0.5 mg/day (higher for transition patients)
- Age 30-60 years: 0.2-0.3 mg/day
- Age > 60 years: 0.1-0.2 mg/day

*Use lower GH doses (0.1-0.2 mg/day) in patients with concurrent DM, obesity, older age, and previous gestational DM*
Recommendations on restarting and maintaining GH replacement in transition patients

- Resume GH at 50% of the dose
- Monitor serum IGF-I
- GH dose adjusted based on clinical response, serum IGF-I levels, side-effects and individual patient considerations
- Measure height, weight, BMI and waist circumference annually
- Measure BMD and lipid profiles Q2-5 years
- Assess QoL using specific QoL-AGHDA questionnaires
Factors that can affect changes in GH dosing

<table>
<thead>
<tr>
<th>↑ dose</th>
<th>↓ dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Young patients regardless of onset type</td>
<td>Elderly</td>
</tr>
<tr>
<td>Low serum IGF-I levels</td>
<td>High serum IGF-I levels</td>
</tr>
<tr>
<td>Addition of oral estrogen</td>
<td>Discontinuation of oral estrogen</td>
</tr>
<tr>
<td>Change from transdermal to oral estrogen</td>
<td>Change from oral to transdermal estrogen</td>
</tr>
<tr>
<td></td>
<td>Worsening glucose tolerance</td>
</tr>
<tr>
<td></td>
<td>Side-effects (e.g., muscle and joint pains)</td>
</tr>
</tbody>
</table>

Consider increasing glucocorticoid (especially when doses are small) and thyroid hormone doses
Use IGF-I as a biomarker for GH dosing

• Aim for serum IGF-I levels between IGF-I SDS -1 and +1

• Consider a trial of higher GH doses to determine whether this provides further benefit as long as the serum IGF-I levels remain within target range and the patient does not experience side-effects

• Do not use IGF-I as the only determinant; also consider body composition, glucose, lipids and QoL changes

• Be aware of differences and changes in IGF-I assays

Johannsson et al on behalf of the GRS. Endocr Connect 2018;7:R126-R134
Why target IGF-I SDS between -1 and +1 SDS?

- High-normal IGF-I (+1 and +2 SDS) waist circumference ↓ and QoL ↑ compared to low-normal IGF-I (-2 and -1 SDS)
- High-normal IGF-I more myalgia
- Low-normal IGF-I more fatigue

- Females with low-normal IGF-I better working memory and strategic memory control
- Females with low-normal IGF-I more fatigue and less vigor
Recommendations for monitoring GH replacement therapy in adults with GHD

• 6- to 12-month intervals

• Monitoring should include clinical evaluation and assessment of side-effects

• If initial bone DXA scan abnormal, repeat at 2- to 3-year intervals

• If a pituitary lesion present, periodic MRIs should be performed

• Patients on concurrent thyroid and GC replacement may need dose adjustments after starting GH therapy

• Patients not already on thyroid or GC replacement should be monitored for the possibility of deficiencies, with replacement given if needed
Parameters to monitor in adults with GHD on GH replacement therapy

Metabolic variables
Body composition (BMI, waist circumference), BMD (DXA scan), CV (blood pressure, pulse rate), lipids, glucose* and IGF-I*

Quality of life
QoL-AGHDA questionnaires

Assessment for side-effects
Including monitoring for potential tumor growth with MRIs*

Assessment and management of other pituitary hormone deficiencies*

*Items marked with an asterisk (*) are required for safety monitoring and should be assessed regularly
Length of GH replacement therapy

• **Indefinitely** if benefits are achieved, but if no benefits > 12 months, discontinuing rhGH therapy may be considered

• If patients discontinue GH replacement therapy, a 6-month follow-up appointment is recommended
Can GH be used during conception and pregnancy?
Recommendations on GH use during conception and pregnancy

- Not approved

- Several studies support use of GH while seeking fertility, as continuing GH during pregnancy does not appear to impact outcomes of either mother or fetus

- More data still needed regarding safety of GH before its routine use in women with GHD to assist conception and its continued use during pregnancy can be recommended
How safe is long-term GH replacement therapy?
Recommendations on GH use in “susceptible” populations

- Patients with DM and glucose intolerance – use low GH doses
- Patients with a history of active malignancy and proliferative diabetic retinopathy - contraindicated
- Patients with strong FH of cancer – careful consideration
- Patients with previous history of cancer – careful consideration based on each individual circumstance after discussion with oncologist, and use low GH doses initiated > 2 years after cancer remission

No evidence GH therapy worsens active malignancy, we just assume this based on studies in acromegaly patients and based on FDA decision to make GH treatment contraindicated in patients with history of active malignancy
Can GH be used for sports and anti-aging?

Absolutely not!
What are the recent developments in this field?
Why consider long-acting GH preparations?

Problems with daily GH injections

- Inconvenient, painful and distressing
- Non-adherence to daily injections increases over time
- Life circumstances can interfere with adherence

By decreasing injection frequency, long-acting GH preparations may improve adherence and thereby potentially maximize clinical efficacy.
# Long-acting GH preparations

<table>
<thead>
<tr>
<th>Company/Lab</th>
<th>Product</th>
<th>Modification to the GH molecule</th>
<th>Frequency of administration</th>
<th>Current status</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Depot formulations</strong></td>
<td></td>
<td></td>
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<tr>
<td>Genentech</td>
<td>Nutropin Depot</td>
<td>Encapsulated in biocompatible, biodegradable, poly(lactide-co-glycolide) polymer microspheres</td>
<td>14 days</td>
<td>Removed from the market</td>
</tr>
<tr>
<td>LG Life Sciences, Ltd.</td>
<td>LB3002</td>
<td>Microparticles containing GH incorporated into sodium hyaluronate and dispersed in an oil base of long-chain triglycerides</td>
<td></td>
<td>Approved in Korea for adult growth hormone deficiency (AGHD); Approved in China, but not marketed in the US</td>
</tr>
<tr>
<td>Altus Pharmaceuticals</td>
<td>ALTU-238</td>
<td>Protein crystallization technique柴田13341; Glycopeptide developed by the company</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Critical Pharmaceuticals</td>
<td>CF016</td>
<td>Supercritical carbon dioxide drying technique; Glycopeptide developed by the company</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>PEGylated formulations</strong></td>
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<td></td>
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</tr>
<tr>
<td>Ambrx</td>
<td>ARX201</td>
<td>PEGylation at the C-terminus of the GH molecule</td>
<td>30-100 days</td>
<td>No longer being developed</td>
</tr>
<tr>
<td>Novo Nordisk A/S</td>
<td>NNCI26-0083</td>
<td>No change to the GH molecule</td>
<td></td>
<td>No longer being developed</td>
</tr>
<tr>
<td>Pfizer</td>
<td>PEG-GH PHAT-012</td>
<td>PEGylation at the C-terminus of the GH molecule</td>
<td>7 days (planned)</td>
<td>No longer being developed</td>
</tr>
<tr>
<td>Bolder BioTechnology</td>
<td>BBT-031</td>
<td>PEGylation at the C-terminus of the GH molecule</td>
<td>7 days</td>
<td>Preclinical studies</td>
</tr>
<tr>
<td>GeneScience</td>
<td>Jintropin</td>
<td>PEGylation at the C-terminus of the GH molecule</td>
<td>7 days</td>
<td>Marketed in China for children with growth hormone deficiency</td>
</tr>
<tr>
<td>Pharmaceuticals Co., Ltd.</td>
<td></td>
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<tr>
<td><strong>Pro-drug formulations</strong></td>
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<tr>
<td>Ascendis</td>
<td></td>
<td>Prodrug formulation via a self-cleaving peptide fusion</td>
<td>7 days</td>
<td>Phase 2 studies in children and adults</td>
</tr>
<tr>
<td><strong>Non-covalent albumin binding</strong></td>
<td></td>
<td></td>
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<tr>
<td>Novo Nordisk A/S</td>
<td></td>
<td>Non-covalent albumin fusion via a self-cleaving peptide fusion</td>
<td>7 days</td>
<td>Phase 2 studies in children and Phase 3 studies in dults</td>
</tr>
<tr>
<td><strong>GH fusion proteins</strong></td>
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<tr>
<td>Hannubilab</td>
<td>LAPSrhGH/HM10560A</td>
<td>Protein fused with GH binding protein</td>
<td>One month (planned)</td>
<td>Preclinical studies</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hybridization of non-cytolytic immunoglobulin Fc portions of IgD and IgG4</td>
<td>7-14 days</td>
<td>Phase 2 studies in adults</td>
</tr>
<tr>
<td>OPKO Health Pharma, Inc.</td>
<td>MOD-4023</td>
<td>Homodimeric aglycosylated IgG4 Fc fragment</td>
<td>7-14 days</td>
<td>Phase 2 in adults</td>
</tr>
<tr>
<td>Teva</td>
<td>TV-1106</td>
<td>Carboxyl-terminal peptide (CTP) of hCG β-subunit</td>
<td>7 days</td>
<td>Phase 2 studies in children and Phase 3 studies in adults</td>
</tr>
<tr>
<td>Versartis</td>
<td>VRS-317</td>
<td>Albumin + XTEN sequence: naturally occurring hydrophilic amino acids</td>
<td>7 days</td>
<td>Trials have been discontinued</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>7-14 days</td>
<td>Phase 3 studies in children and Phase 2 studies in adults</td>
</tr>
</tbody>
</table>
Key points (1)

- Effective management of adult GHD is not an exact science and the new guidelines provide a framework for improved patient care.
- Sustained benefits and long-term safety of GH replacement have been demonstrated.
- Diagnosing adult GHD requires clinical judgment, measurement of IGF-I levels, and use of appropriate GH stimulation test/s.
- GH replacement therapy should be individualized based on symptoms, biomarkers, and avoidance of AEs.
Key points (2)

• To improve the GST diagnostic accuracy in overweight/obese patients, a lower GH cut-point of 1 μg/L is recommended.

• Oral macimorelin, now FDA-approved, will likely be the preferred alternative test to the ITT.

• Aim for serum IGF-I levels between IGF-I SDS -1 and +1 appropriate for age and sex, unless side-effects prohibit.

• Daily GH injections can be burdensome, leading to non-adherence, and long-acting GH preparations currently being developed might address these important issues.
THANK YOU FOR YOUR ATTENTION!