Growth Hormone Replacement Therapy: Optimizing Patient Outcomes in Managed Care

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Talking Points

- Briefly review the clinical and psychosocial benefits of growth hormone replacement therapy
- Discuss adherence to long-term GH therapy in children and adults
- Identify adherence-promoting strategies
Growth Hormone Deficiency in Adulthood

- Approximately 50,000 adults in the US have GHD
  - 6,000 new cases are reported each year, including GHD children who transition to GHD as an adult
- Categories based on the time GHD became manifest
  - **Adult-onset (acquired) GHD:** caused by trauma, central nervous system infection, hypothalamic or pituitary tumors, infiltrative or granulomatous disease, cranial irradiation, surgery, etc.
  - **Pediatric Organic GHD:** caused by genetic or acquired defects which continue into adulthood
  - **Child-onset idiopathic:** childhood GHD of unknown cause that may or may not continue into adulthood

Clinical and Emotional Impact of Growth Hormone Deficiency

<table>
<thead>
<tr>
<th>Physical&lt;sup&gt;1-4&lt;/sup&gt;</th>
<th>Metabolic&lt;sup&gt;1-6&lt;/sup&gt;</th>
<th>Psychosocial&lt;sup&gt;7&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Reduced bone mineral density</td>
<td></td>
<td></td>
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<tr>
<td>• Reduced lean body mass</td>
<td></td>
<td></td>
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<tr>
<td>• Increased body fat</td>
<td></td>
<td></td>
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<tr>
<td>• Excessive fatigue</td>
<td></td>
<td></td>
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<tr>
<td>• Limited ability to perform daily activities</td>
<td></td>
<td></td>
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<tr>
<td>• Abnormal lipid profile</td>
<td></td>
<td></td>
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<tr>
<td>• Increased cardiovascular risk</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Abnormal body composition</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Reduced bone density</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Poor immune function</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Reduced quality of life</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Emotional disturbances</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Reduced self-confidence</td>
<td></td>
<td></td>
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<tr>
<td>• Social isolation</td>
<td></td>
<td></td>
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<tr>
<td>• Impaired memory and concentration</td>
<td></td>
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</tr>
</tbody>
</table>

GH-Deficient Adults Are at Greater Risk for CVD and Other Chronic Conditions

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Evidence of Morbidity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone density</td>
<td>Three-fold increase in bone fracture frequency(^1)</td>
</tr>
<tr>
<td>Atherosclerosis</td>
<td>Over 20% increased carotid intima thickness(^2)</td>
</tr>
<tr>
<td>Inflammation</td>
<td>Two-fold increase in inflammatory markers CRP and IL-6(^3)</td>
</tr>
<tr>
<td>Body composition</td>
<td>Greater adiposity, lower muscle strength(^4)</td>
</tr>
<tr>
<td>Quality of life</td>
<td>Impaired quality of life compared with the general population(^5)</td>
</tr>
</tbody>
</table>


CVD=cardiovascular disease  
CRP=C-reactive protein  
IL=interluekin
GH Therapy Alters Multiple Cardiometabolic Variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline</th>
<th>After 6 Mo GH Therapy</th>
<th>Change from Baseline (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting insulin (mU/mL)</td>
<td>3.5</td>
<td>3.1*</td>
<td>-11</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>6.2</td>
<td>5.6*</td>
<td>-9.7</td>
</tr>
<tr>
<td>C-reactive protein (mg/dL)</td>
<td>7.02</td>
<td>4.81</td>
<td>-31.5</td>
</tr>
<tr>
<td>Fasting plasma glucose (mg/dL)</td>
<td>94.8</td>
<td>91.7</td>
<td>-3.3</td>
</tr>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td>209.5</td>
<td>185.5†</td>
<td>-11.5</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>153.7</td>
<td>125.5</td>
<td>-18.3</td>
</tr>
<tr>
<td>Lp(a) (mg/dL)</td>
<td>15.3</td>
<td>21.3</td>
<td>40.2</td>
</tr>
</tbody>
</table>

n=20 adult GHD patients  
Mean age=46 years  
Initial and final doses:  
0.33 and 0.38 mg/kg (women, n=10)  
0.25 and 0.35 mg/kg (men, n=10)  

*Changes are not clinically significant  
†P<0.05  
Quality of Life in GH-Deficient Adults Improves With GH Replacement Therapy

Data from the KIMS International Metabolic Database


KIMS=Kabi International Metabolic Study
12 Months of GH Therapy Reduced the Need for Health Care

Data from the KIMS International Metabolic Database

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>12 Months</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sick leave days</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(number in previous 6 months)</td>
<td>9.5</td>
<td>3.8*</td>
</tr>
<tr>
<td><strong>Hospital days</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(number in previous 6 months)</td>
<td>1.7</td>
<td>0.6*</td>
</tr>
<tr>
<td><strong>Doctor visits</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(number in previous 6 months)</td>
<td>2.1</td>
<td>1.4†</td>
</tr>
<tr>
<td><strong>Leisure time physical activity</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(visual analog scale score)</td>
<td>40.8</td>
<td>51.1‡</td>
</tr>
<tr>
<td><strong>Satisfaction with leisure time activities</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(visual analog scale score)</td>
<td>41.6</td>
<td>48.8‡</td>
</tr>
<tr>
<td><strong>Need for assistance with daily activities (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>21</td>
<td>16*</td>
</tr>
</tbody>
</table>

*P<0.05 vs baseline  †P<0.01 vs baseline  ‡P<0.001 vs baseline

n=150 and 154 adult men and women with GHD, respectively.
Mean ages: Men 51 years; women: 49 years.
None of the patients had received prior GH therapy in adulthood.
GH dose ranged from 0.042 mg/kg/wk to 0.083 mg/kg/wk.

Growth Hormone Deficiency and Other Forms of Short Stature in Childhood

- Approximately 1 in 3,500 children in the US carries a diagnosis of growth hormone deficiency (GHD)\textsuperscript{1}
  - 20% have organic GHD resulting from central nervous system tumors, radiation, infection, or traumatic brain injury
  - 80% have idiopathic GHD with no known cause

<table>
<thead>
<tr>
<th>Definition</th>
<th>Maximum Estimated Prevalence*</th>
</tr>
</thead>
<tbody>
<tr>
<td>ISS\textsuperscript{2} Height ≥2.25 standard deviations below the mean for age and gender without evidence of underlying disease or GHD</td>
<td>400,000</td>
</tr>
<tr>
<td>SGA\textsuperscript{3} Birth weight and/or length at ≥2 standard deviations below the mean for gestational age and height below -2 SDS at age 4</td>
<td>90,000</td>
</tr>
</tbody>
</table>

*Actual number of patients presenting to endocrinologists is approximately 10-fold lower.


ISS=idiopathic short stature
SGA=small for gestational age
# GH Therapy in Children Born Small for Gestational Age Increases Adult Height

## Meta-analysis of 5 Randomized Controlled Clinical Trials

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Treated</th>
<th></th>
<th></th>
<th></th>
<th>Weight</th>
<th>Mean Difference</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Total</td>
<td>Mean</td>
<td>SD</td>
<td>Total</td>
<td>IV, Random [95% Cl]</td>
</tr>
<tr>
<td>Carel et al&lt;sup&gt;11&lt;/sup&gt; (2003)</td>
<td>-2.1</td>
<td>1.0</td>
<td>102</td>
<td>-2.7</td>
<td>0.9</td>
<td>47</td>
<td>21.3%</td>
</tr>
<tr>
<td>Dahlgren and Wikland&lt;sup&gt;10&lt;/sup&gt; (2005) &lt;2 y</td>
<td>-1.6</td>
<td>0.8</td>
<td>41</td>
<td>-2.0</td>
<td>0.8</td>
<td>34</td>
<td>20.2%</td>
</tr>
<tr>
<td>Dahlgren and Wikland&lt;sup&gt;10&lt;/sup&gt; (2005) &gt;2 y</td>
<td>-1.2</td>
<td>0.7</td>
<td>36</td>
<td>-2.0</td>
<td>0.8</td>
<td>34</td>
<td>20.5%</td>
</tr>
<tr>
<td>Van Dijk et al&lt;sup&gt;13&lt;/sup&gt; (2007)</td>
<td>-1.4</td>
<td>1.0</td>
<td>37</td>
<td>-2.6</td>
<td>0.6</td>
<td>25</td>
<td>19.2%</td>
</tr>
<tr>
<td>Van Pareren et al&lt;sup&gt;12&lt;/sup&gt; (2003)</td>
<td>-1.0</td>
<td>0.8</td>
<td>54</td>
<td>-2.3</td>
<td>0.7</td>
<td>15</td>
<td>18.8%</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td></td>
<td></td>
<td>270</td>
<td></td>
<td></td>
<td>155</td>
<td>100%</td>
</tr>
</tbody>
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Heterogeneity: $\tau^2=0.10$; $\chi^2=15.58$, $df=4$($P=0.004$); $\rho=74\%$

Test for overall effect: $z=5.11$ ($P<0.00001$)

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Efficacy of GH Therapy on the Psychosocial Profile of ISS Children

Child Behavioral Checklist (CBCL) Score by Age

![Bar chart showing CBCL scores by age and gender.

Total Change in CBCL Score After 4 Years of GH Therapy

![Bar chart showing total change in CBCL score by year.

Higher CBCL scores indicate inferior functioning.

*P<0.001 vs control
†P<0.05 vs control


Sample sizes for years 1, 2, 3, and 4: Placebo=9, 19, 9, 3; GH=17, 23, 12, 9, respectively.
Adherence to Growth Hormone Therapy
Up to 50% of Patients May be Non-adherent to Growth Hormone Therapy

- Estimates of non-adherence to GH therapy range from 36% to 49%\(^1-3\)
- Non-adherence is generally more common in adolescents and younger adults\(^4\)

Greater Number of Missed Injections Associated With Lower Growth Rate

Frequency of Missed Injections/Week

- 0/Week: 0.47
- ≤1/Week: 0.47
- >1–2/Week: 0.42
- >2/Week: 0.05

n=75
Mean age=12.3 years
Cross sectional data
Mean duration of GH treatment=1.9 years
GH dose=0.8 mg/kg/day.

36% (27/75) missed 0 injections/week;
25% (19/75) missed ≤1/week;
16% (12/75) missed >1–2/week;
23% (17/75) missed >2 injections/week.

*Adjusted for age and duration of GH
†P<0.05therapy

**Height Velocity (SDS/year)**

<table>
<thead>
<tr>
<th>Frequency of Missed Injections/Week</th>
<th>Height Velocity</th>
</tr>
</thead>
<tbody>
<tr>
<td>0/Week</td>
<td>0.47</td>
</tr>
<tr>
<td>≤1/Week</td>
<td>0.47</td>
</tr>
<tr>
<td>&gt;1–2/Week</td>
<td>0.42</td>
</tr>
<tr>
<td>&gt;2/Week</td>
<td>0.05†</td>
</tr>
</tbody>
</table>
Indicators of Non-adherence: Children and Adolescents

• Increasing gap between predicted and actual growth rates
• Diminished frequency of prescription refills
• Increasing time period between refills
• Failure to show up for follow-up appointments

Indicators of Non-adherence: Adults

• Significant non-adherence (eg, missing >80% of prescribed doses) is reflected in decreased plasma IGF-1 levels
  – More subtle levels of non-adherence (eg, missing <20% of prescribed doses) is unlikely to show up on IGF-1 measurements

• Change in healthcare coverage
  – Higher copay
  – Limited access to preferred administration device

IGF-1=insulin-like growth factor 1

Factors Contributing to Non-adherence

- A review of the literature indicated poor adherence is often associated with
  - Patients' lack of understanding of their disease
  - Patient age
  - Chronicity of the disease
  - Complex treatment regimens
  - Insufficient information on the implications of non-adherence

Poor Adherence: The Patient’s Perspective

• Reasons given by patients for poor adherence include
  – Inconvenience of daily injections for many years\(^1,2\)
  – Discomfort associated with repeated injections\(^2\)
  – Disappointed with treatment outcomes\(^1,2\)
    • Inability to see short-term clinical (ie, height) and psychosocial (ie, quality of life) benefits
  – Difficulties with access and reimbursement\(^1,2\)
    • High out-of-pocket expenses
    • Limited choice of therapy/devices
    • Lag between diagnosis/prescription and starting treatment due to need for authorization

Influence of the GH Administration Device on Adherence

Device Features that Help Patients’ Adherence to Their GH Treatment Regimens

- Easy to use injection device
- Easy to learn injection technique
- Minimal injection pain and needle anxiety

Strategies to Improve Adherence

- Strengthen the patient-physician relationship
- Educate about the disease and the benefits of adherence
- Make a distinction between difficult-to-perceive objective outcomes and subjective benefits that may be more readily noticed
  - Objective: growth rate, change in body composition/metabolic parameters, etc.
  - Subjective: quality of life, energy level, etc.
- Select an injection device that is easy to use
- Devise alternative dosing strategies

Utilize Physician Extenders to Educate Patients and Monitor Adherence

- Extenders may have more time to develop a rapport with the patient and the patient's family
- Specific responsibilities may include
  - Evaluating the growth chart at each visit and discussing what's working and what's not
  - Educating patients on the disease and the importance of adherence
  - Initiating regular contact between clinic visits to ensure adherence

Safety of Long-term GH Therapy and Adherence

- Parents of children prescribed GH as well as adults prescribed GH commonly express concerns about the safety of long-term GH therapy
- Data from GH drug registries extending over 25 years confirm a favorable overall safety profile
  - Patients with no medical history of risks known to increase the risk of cancer were not at a higher cancer risk with GH treatment
  - However, specific populations with pre-existing conditions may be at potential risk

Data from the National Cooperative Growth Study (NCGS) of 54,996 children who receive drhGH.

Summary

- Non-adherence to GH therapy ranges from 36–49% 
  - It is generally lower in younger patients
- Low adherence is associated with poor outcomes
- Reasons for low adherence include duration of therapy, lack of knowledge about the disease, inconvenience of therapy, and cost
- Strategies that may improve adherence include patient education, utilization of a flexible dosing schedule, and treatment with easy-to-use GH administration devices