Growth Hormone Replacement Therapy: Clinical and Economic Implications for Managed Care

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Talking Points

• Review clinical and economic data on recombinant human growth hormone (rhGH) therapy for adults and children with growth hormone deficiency (GHD) and related disorders, including:
  – Outcomes
  – Cost
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(^1-4)</th>
<th>Metabolic(^1-6)</th>
<th>Psychosocial(^7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Reduced bone mineral density</td>
<td>• Abnormal lipid profile</td>
<td>• Reduced quality of life</td>
</tr>
<tr>
<td>• Reduced lean body mass</td>
<td>• Increased cardiovascular risk</td>
<td>• Emotional disturbances</td>
</tr>
<tr>
<td>• Increased body fat</td>
<td>• Abnormal body composition</td>
<td>• Reduced self-confidence</td>
</tr>
<tr>
<td>• Excessive fatigue</td>
<td>• Reduced bone density</td>
<td>• Social isolation</td>
</tr>
<tr>
<td>• Limited ability to perform daily activities</td>
<td>• Poor immune function</td>
<td>• Impaired memory and concentration</td>
</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&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>Atherosclerosis</td>
<td>Over 20% increased carotid intima thickness&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>Inflammation</td>
<td>Two-fold increase in inflammatory markers CRP and IL-6&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
<tr>
<td>Body composition</td>
<td>Greater adiposity, lower muscle strength&lt;sup&gt;4&lt;/sup&gt;</td>
</tr>
<tr>
<td>Quality of life</td>
<td>Impaired quality of life compared with the general population&lt;sup&gt;5&lt;/sup&gt;</td>
</tr>
</tbody>
</table>


CVD=cardiovascular disease
CRP=C-reactive protein
IL=interleukin
Elevated Cholesterol Adds to the CVD Risk in Adult GHD

**GH Therapy Has Significant Beneficial Effects on Cholesterol, Blood Pressure**

<table>
<thead>
<tr>
<th>Factors</th>
<th>Treatment</th>
<th>Weighted mean change (GH-placebo)</th>
<th>Global Effect Size (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lean B mass</td>
<td>GH 473</td>
<td>2.82 kg</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Placebo 474</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fat mass</td>
<td>GH 352</td>
<td>3.05 kg</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Placebo 345</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td>GH 134</td>
<td>-0.12 kg/m²</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Placebo 134</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TG</td>
<td>GH 202</td>
<td>2.71 mg/dL</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Placebo 203</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HDL Chol.</td>
<td>GH 267</td>
<td>2.32 mg/dL</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Placebo 261</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDL Chol.</td>
<td>GH 255</td>
<td>-20.50 mg/dL</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Placebo 248</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Chol.</td>
<td>GH 310</td>
<td>-13.15 mg/dL</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Placebo 306</td>
<td></td>
<td></td>
</tr>
<tr>
<td>D.B.P.</td>
<td>GH 200</td>
<td>-1.80 mmHg</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Placebo 201</td>
<td></td>
<td></td>
</tr>
<tr>
<td>S.B.P.</td>
<td>GH 190</td>
<td>2.06 mmHg</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Placebo 191</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin</td>
<td>GH 192</td>
<td>1.2 IU/mL</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Placebo 194</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glucose</td>
<td>GH 254</td>
<td>8.51 mg/dL</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Placebo 257</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

GH=growth hormone  
BMI=body mass index  
LDL=low density lipoprotein  
TG=triglyceride  
HDL=high density lipoprotein  
Chol=cholesterol  
DBP=diastolic blood pressure  
SBP=systolic blood pressure

# 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>

- Changes are not clinically significant
- *P*<0.05

Quality of Life in Adults With GHD Is Significantly Worse vs General Population

Data from the KIMS International Metabolic Database

- **KIMS Database (n=836)**
- **General Population (n=921)**

<table>
<thead>
<tr>
<th>Gender</th>
<th>KIMS Database</th>
<th>General Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males</td>
<td>13.6</td>
<td>6.2</td>
</tr>
<tr>
<td>Females</td>
<td>15.7</td>
<td>7.1</td>
</tr>
<tr>
<td>Total</td>
<td>14.7</td>
<td>6.7</td>
</tr>
</tbody>
</table>

*Lower scores on the QoL-AGHDA indicate a higher quality of life
†P<0.001 vs patients in the KIMS database
Quality of Life in GH-Deficient Adults Improves With GH Replacement Therapy

Data from the KIMS International Metabolic Database

Difference in mean (95% CI) QoL-AGHDA score

--- Reference population (n=1682)
- KIMS patients

KIMS=Kabi International Metabolic Study

Very Low BMD in Adults With Severe GHD

Mean GH (µ/L) 40.7, 28.3, and 0.9 for control, non-GHD, and severe GHD, respectively

*P<0.01
Bone Mineral Density in GHD Adults Increases With GH Therapy

Effects of 10 Years of GH Therapy in GHD 87 Adults

-0.18 -0.21 -0.1 -0

Total Body BMD T-score

Mean GH dose (mg/d)  Baseline  1 Year  3 Years  5 Years  7 Years  10 Years
0.98  0.66  0.53  0.50  0.48  0.47

BMD=bone mineral density

* p<0.001 vs baseline

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

- 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.

*P<0.05 vs baseline
†P<0.01 vs baseline
‡P<0.001 vs baseline
24 Months of GH Replacement
Reduced Sick Leave Days

148 Adult GHD Patients (mean age = 43.5 yr) Treated
With rhGH (1.25 IU/m2/d) for 24 Months

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

Shift in Use for GH Therapy Indicates a Trend Toward Less Severe Forms of GHD

Decreasing Trends

GH-treated Patients (n = 5893)

- Pituitary adenoma
- Cranio-pharyngioma
- Pituitary intracranial tumor
- Pituitary hemorrhage

<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>Pituitary adenoma</td>
<td>13%</td>
<td>8%</td>
</tr>
<tr>
<td>Cranio-pharyngioma</td>
<td>6%</td>
<td>7%</td>
</tr>
<tr>
<td>Pituitary intracranial tumor</td>
<td>50%</td>
<td>39%*</td>
</tr>
<tr>
<td>Pituitary hemorrhage</td>
<td></td>
<td>8%†</td>
</tr>
</tbody>
</table>

Increasing Trends

- Undefined/unknown causes
- Less common diagnoses
- Idiopathic

<table>
<thead>
<tr>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Undefined/unknown causes</td>
<td>1%</td>
<td>7%</td>
</tr>
<tr>
<td>Less common diagnoses</td>
<td>14%</td>
<td>9%*</td>
</tr>
<tr>
<td>Idiopathic</td>
<td>16%*</td>
<td>20%*</td>
</tr>
</tbody>
</table>

*P<0.001 vs 1996–1997
†P=0.005 vs 1996–1997
‡P=0.001 vs 1996–1997

Adult GHD: Summary

• Adults with GHD are at increased risk for cardiovascular disease, impaired physical function, and reduced quality of life.
• It is recommended that GH be prescribed for adults with a history of hypothalamic-pituitary disease and biochemically proven GHD.
  – GH therapy appears to have a beneficial effect on bone, muscle, cardiovascular risk, quality of life and other variables.
  – However, data on the effect of GH therapy on endpoints such as cardiovascular events, fractures, and death are lacking.
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)\(^1\)
  - 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>Additional FDA-approved Indications for GH Therapy in Children</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Definition</strong></td>
</tr>
<tr>
<td>ISS(^2)</td>
</tr>
<tr>
<td>SGA(^3)</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
Long-term GH Therapy Is Beneficial to Patients With Genetically-Mediated Short Stature

24 Months of GH Effective for Treating Short Stature Associated With SHOX-D and Turner Syndrome

SHOX-D=short stature homeobox-containing gene deficiency


SHOX-D group: n=52 (aged 3.0–12.3 yrs)
Turner Syndrome group: n=26 (aged 4.5–11.8 yrs)
All patients received GH 50 mg/kg/day via sc injection
GH Therapy Reduces Body Fat and Increases Height in Patients With Genetically-Mediated Short Stature

Significantly Lower Body Fat and Greater Height Following 6 Years of GH Therapy in Children With Prader-Willi Syndrome

*P<0.01 vs control
†Aged 6–9 yrs at baseline
‡Aged 5–9 yrs at baseline

Dose-related Responses of Height and IGF-1 to 2 Years of GH Therapy in GH-Deficient Boys

Plots represent +/- 2 SD (error bars), the 25 and 75% (box), the mean (red square), and the median (horizontal bar).

SDS=standard deviation score
IGF-1=insulin-like growth factor 1

Long-term GH Therapy in Children With CKD Results in an Increased Adult Height

Data From the Pfizer International Growth Database (KIGS)

Boys: n=193; aged 4.7–19.7 years; Girls: n=47; aged 8.1–18.0 years.
All patients received GH (target dose 0.33 mg/kg/week) for at least 1 year.

CKD=chronic kidney disease

#P<0.01 boys vs girls
*P<0.01 vs previous time point
### Meta-analysis of 5 Randomized Controlled Clinical Trials

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Treated</th>
<th>Untreated</th>
<th>Weight</th>
<th>Mean Difference</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>SD</td>
<td>Total</td>
<td>Mean</td>
<td>SD</td>
<td>Total</td>
</tr>
<tr>
<td>Carel et al(^{11}) (2003)</td>
<td>-2.1</td>
<td>1.0</td>
<td>102</td>
<td>-2.7</td>
<td>0.9</td>
</tr>
<tr>
<td>Dahlgren and Wikland(^{10}) (2005) &lt;2 y</td>
<td>-1.6</td>
<td>0.8</td>
<td>41</td>
<td>-2.0</td>
<td>0.8</td>
</tr>
<tr>
<td>Dahlgren and Wikland(^{10}) (2005) &gt;2 y</td>
<td>-1.2</td>
<td>0.7</td>
<td>36</td>
<td>-2.0</td>
<td>0.8</td>
</tr>
<tr>
<td>Van Dijk et al(^{13}) (2007)</td>
<td>-1.4</td>
<td>1.0</td>
<td>37</td>
<td>-2.6</td>
<td>0.6</td>
</tr>
<tr>
<td>Van Pareren et al(^{12}) (2003)</td>
<td>-1.0</td>
<td>0.8</td>
<td>54</td>
<td>-2.3</td>
<td>0.7</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td></td>
<td></td>
<td>270</td>
<td>155</td>
<td>100%</td>
</tr>
</tbody>
</table>

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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Maiorana A, Cianfarani S. *Pediatrics.* 2009;124(3);e519–e531.
SGA Children Without Spontaneous Catch-up Growth Benefit From GH Treatment


- **Group I <4 yrs (60 μg/kg/d for 2 yrs)**
- **Group I ≥4 yrs (60 μg/kg/d for 2 yrs)**
- **Group II <4 yrs (12 mos with no treatment; GH for 12 mos)**

**Cumulative Height SDS Chronological Age Gain**

- Baseline
- +6
- +12
- +18
- +24 mos

*P*<0.05 Group I <4 years vs Group I ≥4 years
†*P*<0.05 Group I <4 years vs Group II <4 and ≥4 years
‡*P*<0.05 Group I ≥4 years vs Group II <4 and ≥4 years
§*P*<0.05 Group I ≥4 years vs Group II ≥4 years

n=16
n=18
n=23
n=16
GH Therapy Normalized BMD in Children Born Small for Gestational Age

*P<0.001 vs placebo
Height Is Greater in GH-treated Idiopathic Short Stature Patients vs Controls

Treatment Duration (years)

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

Efficacy of GH Therapy on the Psychosocial Profile of ISS Children

Child Behavioral Checklist (CBCL) Score by Age

- Normal
- GHD (n=127)
- ISS (n=116)

Higher CBCL scores indicate inferior functioning.

Total Change in CBCL Score After 4 Years of GH Therapy

- Placebo
- GH

(32 μg/kg/d)

*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.
Childhood GHD: Summary

• 1 in 3,500 children in the US are diagnosed with GHD
  – Only 20% have organic GHD; readily identifiable cause absent in the majority of cases
• Approximately 90,000 infants are born SGA in the US annually
  – GH treatment in SGA include increased final adult height and bone mineral density
  – GH therapy can be a cost-effective treatment for SGA
• Approximately 400,000 children in the US have ISS
  – GH therapy increases height and may improve behavioral profile of children with ISS
  – However, no consensus exists on the use of GH in ISS