Approved indications for Growth Hormone Therapy

Allometric model of human growth

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The discovery of growth hormone (GH)

1887: Minkowski observes enlarged sella in cases of acromegaly (first scientific account in 1772)

1894: Cushing performs transsphenoidal removal of pituitary of a farmer with acromegaly

The patient survives for 21 years

1922: Evans and Long injected beef pituitary extract to animals (rats) and reported excessive growth.
The discovery of growth hormone (GH)

1908: Houssay shows that the growth-promoting pituitary factor has diabetogenic effects (won Nobel Prize in 1947)

1932: first publication of treatment of children with highly purified pituitary extracts. Utterly discouraging results (extremely high doses needed).

1944: Li and Evans isolated bovine GH

1957: Daughaday concluded that GH action was mediated through a factor which was named somatomedin (mediates the effects of somatotropin)

1957: Raben successfully treated a 16-yo « dwarf »
The discovery of growth hormone (GH)

By 1985, more than 6000 patients had been treated with GH in the US alone.

In 1979, production of rhGH (Genentech, Inc.)
The biological properties of GH

191 amino-acids
4 helices

Nature Reviews Endocrinology 6, 515-525 (September 2010)
The biological properties of GH

Question #1:

Regarding GH, all these affirmations are correct, except one:

A. GH stimulates the proliferation of bone cartilage (growth plates)
B. GH increases muscle mass
C. GH secretion is stimulated by exercise
D. GH secreting cells are the most important in pituitary
E. GH stimulates lipolysis (↑ fatty acids in blood)
The biological properties of GH

- Stress
- Exercise
- Starvation
- Acute hypoglycemia
- Aging

GHRH neuron

GH

Pituitary

Phases 3-4 of sleep

GH secretion rate (μg/min)

Time relative to sleep onset (Hours)
The biological properties of GH

GH stimulates:
- growth of bones
- protein synthesis
- DNA synthesis via IGF-1

ALS = acid-labile subunit
The biological properties of GH
The biological properties of GH

Metabolic activities:
- Stimulate lipolysis
- Glucose consumption
- Neoglucogenesis

Anti-insulin effects

Nature Clinical Practice Endocrinology & Metabolism (2006) 2, 436-446
Clinical indications of rhGH therapy

In 1990, the US Congress passed an omnibus crime bill, the Crime Control Act of 1990:

« Off-label use of rhGH is illegal »

The FDA, as recently as 2012, has issued alerts stating that

« FDA-approved HGH can be legally prescribed for a limited number of conditions »
Clinical indications of rhGH therapy

Question #2:

**GH** can be *legally* prescribed for (all affirmations are incorrect except one):

A. Idiopathic short stature
B. Increasing muscle mass in ageing patients
C. Improving bone density both in children and adults
D. Precocious puberty in girls
E. Children born small for gestational age
<table>
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<tr>
<th>History</th>
<th>GH biology</th>
<th>Clinical indications of rhGH</th>
<th>Outcomes</th>
<th>Conclusion</th>
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</table>

**Clinical indications of rhGH therapy**

1. Growth hormone deficiency (pediatric & adult) 60%
2. Small for gestational age 20%
3. Chronic renal insufficiency 3%
4. Turner syndrome (Noonan syndrome) 15%
5. Prader-Willi syndrome 2%
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<tr>
<td></td>
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<td>GH deficiency</td>
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</table>

Idiopathic (55%) / Congenital (cleft palate, median tooth) / Secondary / Genetic
GH deficiency

Idiopathic GHD
Organic GHD
Congenital form
  Genetic cause (Pit-1, GH1, HESX-1 defect)
  Central malformation
    HME¹
    Other²
    Other³
Acquired GHD
  Cranial tumour of the pituitary-hypothalamus area⁴
    Irradiated
    Non-irradiated
  Cranial tumour distant from pituitary-hypothalamus
    Irradiated
    Non-irradiated
  Treatment for malignancy
    Acute lymphatic leukaemia
    Lymphoma and others
  Other causes of acquired GHD
  Syndromes with concomitant GHD

>30 Gy
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<tr>
<td><strong>History</strong></td>
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</tr>
<tr>
<td>traumatic birth delivery</td>
<td>low IGF-1 levels (half-life= 24 hours)</td>
<td>low IGF-1 levels (half-life= 24 hours)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>neonate: hypoglycemia, micropenis, prolonged jaundice</td>
<td>associated hormonal deficiencies</td>
<td>associated hormonal deficiencies</td>
<td>5 y</td>
<td>11 y</td>
</tr>
<tr>
<td>irradiation, trauma, infection, consanguinity with history of GHD</td>
<td></td>
<td></td>
<td>5 y</td>
<td>11 y</td>
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<tr>
<td>midline defects</td>
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<tr>
<td>extremely short stature (&lt;-3 SD)</td>
<td></td>
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<td></td>
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<tr>
<td>growth velocity &lt;-1 SD</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>co-morbidities</td>
<td></td>
<td></td>
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<tr>
<td>Biology</td>
<td></td>
<td></td>
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<tr>
<td>Clinical indications of rhGH: diagnosis</td>
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<td>Outcomes</td>
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</table>
GH deficiency: diagnosis – clinical exam

**Height**
WHO charts =
Norway, USA, Oman, Brasil,
India, Ghana

**Weight / BMI / H.C. / arm span /**
Disproportions / dysmorphism
GH deficiency: diagnosis – clinical exam

Height
WHO charts =
Norway, USA, Oman, Brasil,
India, Ghana

Weight / BMI / H.C. / arm span / sitting height
Disproportions / dysmorphism

Tanner
GH deficiency: diagnosis – clinical exam

Girls

<table>
<thead>
<tr>
<th>AGE (years)</th>
<th>HEIGHT (cm)</th>
</tr>
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<tbody>
<tr>
<td>22</td>
<td>200</td>
</tr>
<tr>
<td>20</td>
<td>180</td>
</tr>
<tr>
<td>18</td>
<td>160</td>
</tr>
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<td>16</td>
<td>140</td>
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<td>14</td>
<td>120</td>
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<td>12</td>
<td>100</td>
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<tr>
<td>10</td>
<td>80</td>
</tr>
<tr>
<td>8</td>
<td>60</td>
</tr>
<tr>
<td>6</td>
<td>40</td>
</tr>
</tbody>
</table>

E: Estimated adult height
M: Mothers height SDS
F: Fathers height SDS
T: Target height interval
BE: Flanders 2004

Growth curve
GH deficiency: diagnosis – imaging
Other clinical characteristics of GHD?

- Changes in memory, processing speed and attention
- Lack of well-being, depression, anxiety, social isolation
- Fatigue

- Lack of strength
- Fibromyalgia syndrome, neuromuscular dysfunction

- Central adiposity
- Decreased muscle mass
- Decreased bone density
- Impaired cardiac function

- Decreased insulin sensitivity
- Accelerated atherogenesis with increased carotid intima–media thickness
- Increased low-density lipoprotein
- Prothrombotic state
- Decreased sweating and thermoregulation

Neurological, Muscular, Bone – adipose tissue, Metabolism
Definition of small for gestational age (SGA), intrauterine growth restriction

Weight at birth < 3rd percentile or -2 DS for gestational age (and charts)

Harmonious/symmetrical SGA
   Weight, height and H.C. < -2 DS

Dysharmonious/assymmetrical SGA
   Weight << -2 DS; height and H.C. < -2DS

For which one would you worry more? And why?
IUGR affects approximately 30 million newborns annually (75% in Asia, 20% in Africa, and 5% in Latin America (de Onis, Blössner & Villar, 1998)).
SGA / IUGR

DYSHARMONIOUS

HARMONIOUS
SGA / IUGR

- 3% of newborns
- 10 à 25% of SGA keep a height at 3rd percentile at 2 to 5 years
- Dysmorphic features and development delay may be associated
- Pronostic of final height « limited »
  - Men: ± 150 cm
  - Women: ± 140 cm
- Sometimes associated to precocious puberty
- 5 à 6% develop metabolic syndrome
Karyotype

Simple

G banding

First-line analysis
May find mosaïcism

Molecular

1000x more precise
Analysis without « a priori »
Turner syndrome

- Lymphoedema / recurrent otitis
- Scholar difficulties (nl I.Q.), exuberant
- Dysmorphism / aortic coarctation / renal malformations / ovarian insuff.
- 45,XO; mosaïcism
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Turner syndrome = large clinical spectrum (mosaïcism)

ovarian insufficiency (↑ FSH)
**Prader-Willi syndrome (1:15,000)**

- Lack of paternally-derived imprinted material on chromosome 15q11-q13.

- **Characteristics:**
  - Mild to moderate intellectual disability
  - Severe hypotonia at birth (GHD)
  - Hyperphagia (> 2 years of age) and risk of obesity
  - Repetitive and compulsive behaviors
  - Skin-picking
  - Social Cognition Deficits
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### Growth hormone treatment

- Different brands (Novo Nordisk, Ipsen, Ferring, Pfizer, Sandoz, Eli Lilly) but all same components
- Subcutaneously one per day
- 25-50 µg/kg B.W./day (FDA approves up to 100 µg/kg BW)
- Treatment of associated deficiencies
Efficacy of rhGH therapy

Variable response – 1 cm/yr of treatment (all indications)

Treatment until growth velocity < 2 cm/yr

GeNeSIS 2016
Tolerance to rhGH therapy

- Benign adverse effects

- Long-term adverse effects:
  - cardiovascular
  - oncogenic
Tolerance to rhGH therapy

Rare side effects (1/1000).

- **Bening intracranian hypertension** (pseudotumor cerebri)

- **Femoral epiphyseal fracture** (BMI !)

- **Scoliosis**

- **Glucose intolerance**

- Pancreatitis, cutaneous nævi

- Joint pain, edema, carpal tunnel syndrome
Risks linked to IGF-1 levels (?)

[Graph showing hazard ratio with 95% CI vs. percentile of IGF-1, highlighting risks linked to IGF-1 levels in colorectal, breast, prostate, and osteosarcoma.]

Colorectal
Breast
Prostate
Osteosarcoma
SAGhE

Description of the SAGhE Cohort: A Large European Study of Mortality and Cancer Incidence Risks after Childhood Treatment with Recombinant Growth Hormone

Anthony J. Swerczow a,b  Rosie Cooke a  Kerstin Albertsson-Wikland c  Birgit Borgström d  Gary Butler e,f  Stefano Cianfarani g,h  Peter Clayton i,j  Joël Costa k,l  Annalisa Deodati g  Emmanuel Ecosse k,l  Ruth Gausche m  Claudio Giacomozzi a  Wieland Kiess n  Anita C.S. Hokken Koelega o,p  Claudia E. Kuehni q  Fabienne Landier s,t  Marc Maes k  Primus-E. Mullis t  Roland Pfaffle m  Lars Savendahl u  Grit Sommer v  Muriel Thomas w  Sally Tollnerfield x  Gladys J.R. Zancwijk j  Jean-Claude Carel j

- French study on global mortality
  - 93/6928 observed against
  - 70/6928 expected (general population)

- Bone tumors expected (0.6) < observed (3)
- Cardiovascular expected (2.9) < observed (9)
- Unknown causes expected (6.2) < observed (21)
Risks depend on rhGH dose

**TABLE 3.** Adjusted SMR of GH-treated patients: final Poisson regression model

<table>
<thead>
<tr>
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<th>SMR</th>
<th>(95% CI)</th>
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<tbody>
<tr>
<td>Mean GH dose: 0–20 μg/kg·d</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Mean GH dose: 20–30 μg/kg·d</td>
<td>0.95</td>
<td>(0.58–1.57)</td>
</tr>
<tr>
<td>Mean GH dose: 30–50 μg/kg·d</td>
<td>1.34</td>
<td>(0.52–3.43)</td>
</tr>
<tr>
<td>Mean GH dose: &gt;50 μg/kg·d</td>
<td>2.94</td>
<td>(1.22–7.07)</td>
</tr>
<tr>
<td>Height at initiation of treatment ≥ −2 SDS</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Height at initiation of treatment: −2 to −3 SDS</td>
<td>1.62</td>
<td>(0.69–3.84)</td>
</tr>
<tr>
<td>Height at initiation of treatment: &lt; −3 SDS</td>
<td>2.31</td>
<td>(0.96–5.59)</td>
</tr>
</tbody>
</table>

Adjusted SMR are expressed with reference to the categories of children who received the lowest dose of treatment (0–20 μg/kg·d) or who were the tallest before treatment (≥ −2 SDS). Variables not independently associated with higher mortality and not kept in the final model included treatment duration, overall exposure, and age at initiation of treatment.

Carel JCEM 2012
Primary tumor risk less than expected?

Fig. 3. The overall malignancy SMR in GH treated subjects. Results of meta-analysis according to random model.

Fig. 9. The overall RR of second neoplasm in GH treated subjects. Results of meta-analysis according to random model.

Meta-analysis Deodati 2014
Primary tumor risk less than expected?

Fig. 3. The overall malignancy SMR in GH treated subjects. Results of meta-analysis according to random model.

Fig. 9. The overall RR of second neoplasm in GH treated subjects. Results of meta-analysis according to random model.

Meta-analysis Deodati 2014
Other risk?
Creutzfeldt-Jakob
Origin of growth hormone

October 11, 1948 issue of *Life* magazine.
History of Growth Hormone

Clinical indications of rhGH

Outcomes

Conclusion

Life magazine.
rhGH therapy: cost-benefit ratio

Constantly evaluated (needs registries)

Long-term (costly) studies

Off-label use: safety & ethical concerns