Growth Hormone Therapy: Adverse Effects

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The history of GH therapy

- 1958: Maurice Raben purified GH from cadaver pituitary glands
- 1970: Choh Hao Li first synthesized GH
- 1977-1979: Scientists at Genentech cloned the gene for GH and produced GH in an E.Coli model
- 1985: FDA approves recombinant DNA-derived human GH for children with GHD
- 1985-2003: FDA gradually expands the list of approved indications for GH
<table>
<thead>
<tr>
<th>Year</th>
<th>Condition</th>
<th>Dose</th>
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</thead>
<tbody>
<tr>
<td>1985</td>
<td>Pediatric GH deficiency</td>
<td>0.03 mg/kg/day</td>
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<tr>
<td>1993</td>
<td>Chronic renal insufficiency</td>
<td>0.05 mg/kg/day</td>
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<td>1996</td>
<td>Turner syndrome</td>
<td>0.07 mg/kg/day</td>
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<td>2000</td>
<td>Prader-Willi syndrome</td>
<td>0.05 mg/kg/day</td>
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<td>2001</td>
<td>Small for gestational age</td>
<td>0.05 mg/kg/day</td>
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<tr>
<td>2003</td>
<td>Idiopathic short stature</td>
<td>0.05 mg/kg/day</td>
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<tr>
<td>2008</td>
<td>Noonan syndrome</td>
<td>0.05 mg/kg/day</td>
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</tbody>
</table>
Effects of GH

Figure 42-1 Growth-promoting and anti-insulin effects of growth hormone. IGF-1, insulin-like growth factor 1.
Potential adverse effects of GH therapy

Short-term

- Fluid retention
  - Intracranial hypertension (pseudotumor cerebri)
  - Carpal tunnel syndrome (mainly in GH treated adults)
  - Edema (mainly in GH treated adults)
- Carbohydrate metabolism (insulin resistance)
- Orthopedic complications
  - Progression of pre-existing scoliosis
  - Slipped capital femoral epiphysis
  - Musculoskeletal aches
  - Arthralgia
- Transient gynecomastia
- Increased growth and pigmentation of nevi
- Alteration in hormones secretion
- Pancreatitis
- Sleep apnea
Intracranial hypertension (ICH)
(pseudotumor cerebri)

- **Cause**
  - The physiological antidiuretic effect of hGH with a decrease in glomerular filtration rate
  - Sodium and water retention
  - A mild transitory elevation in plasma renin activity and aldosterone

- **Complaints**
  - Headache
  - Nausea and vomiting
  - Presenting papilledema (+/-)

- **Diagnostic work-up**
  - Fundus examination
  - Brain imaging
  - LP

- **Management** (if the diagnosis of ICH is confirmed)
  - GH should be discontinued temporarily, and reinitiated later on, at lower doses
Potential adverse effects of GH therapy

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Carbohydrate metabolism

- Insulin resistance
  - Increased fasting insulin levels (usually remain within the normal range)
  - Insulin levels return to baseline once GH treatment is withdrawn

- The clinical significance of the decrease in insulin sensitivity during GH treatment appears to be low
  - No increased evidence of impaired glucose tolerance or T2DM in children who are not otherwise predisposed
  - The incidence and age at diagnosis of T1DM during GH treatment is similar to the general population
Potential adverse effects of GH therapy

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- Pancreatitis
- Sleep apnea
Orthopedic complications

Scoliosis (worsening of existing scoliosis)

- Progression of existing scoliosis is accelerated by rapid growth
  - Pubertal growth spurt
  - GH treatment

- Clinical examination of the spine
  - Before start of GH therapy
  - During follow-up of patients receiving GH therapy

- In the presence of scoliosis
  - Should GH therapy be initiated or continued
  - Should radiographic studies be obtained to monitor for any change
Orthopedic complications

Slipped capital femoral epiphysis (SCFE)

- Increased diaphyseal-epiphyseal angle (Southwick’s angle) during GH treatment increases the risk of epiphysiolysis: a posterior and inferior displacement of the proximal femoral epiphysis on the femoral neck

- Complaints - unilateral or bilateral pain in the hips or knees

- Assessment of risk - measurement of the Southwick’s angle using anteroposterior pelvic radiography at the beginning of therapy and annually thereafter

- Treatment - surgical: in-situ screw fixation
Potential adverse effects of GH therapy

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  - Arthralgia
- Transient gynecomastia
- Increased growth and pigmentation of nevi
- Alteration in hormones secretion
- Pancreatitis
- Sleep apnea
Prepubertal gynecomastia

- A rare and self-limited adverse effect of GH treated children

- The time from the initiation of therapy to the diagnosis of gynecomastia 0.5 to 8 years

- Resolution occurs
  - After discontinuation of GH
  - Still in use of GH

- There is no need for
  - Alteration in GH dosage
  - Discontinuation of medication
Alteration in hormones secretion & metabolism

- **Adrenal**
  - GH increases the tissue conversion of active cortisol to inactive cortisone
  - In subclinical ACTH deficiency GH may induce symptomatic adrenal insufficiency requiring glucocorticoid substitution
  - In patients on cortisol replacement dose adjustment may be needed

- **Thyroid**
  - GH increases the peripheral conversion of T4 to T3
  - Commencement of GH replacement may therefore unmask a pre-existing central hypothyroidism
  - In patients taking thyroxine, adjustment of the thyroxine dose may be needed after initiation of GH replacement therapy if a decrease in the serum concentration of free T4 occurs.
  - Thyroid function should be monitored at initiation of GH treatment and after dose increases
Other potential adverse effects...

- Increased growth and pigmentation of nevi\(^1\)
  - GH is able to activate melanocyte proliferation
  - No evidence of malignant transformation of the melanocytic nevi during GH therapy
  - No increase in the incidence of skin cancer in GH treated children

- Sleep apnea
  - GH can stimulate adenotonsillar growth and thereby exacerbate obstructive sleep apnea

- Pancreatitis
  - Severe abdominal pain; increased plasma amylase levels
  - Extremely rare
  - Its causal relationship to GH treatment remains unclear

\(^1\) Wyatt D. Melanocytic nevi in children treated with GH. Pediatrics. 1999
Potential adverse effects of GH therapy

- Fluid retention
  - Intracranial hypertension (pseudotumor cerebri) (<1/1000 treated children)
  - Carpal tunnel syndrome (mainly in GH treated adults)
  - Edema (mainly in GH treated adults)

- Carbohydrate metabolism (insulin resistance)

- Orthopedic complications
  - Progression of pre-existing scoliosis
  - Slipped capital femoral epiphysis
  - Musculoskeletal aches
  - Arthralgia

- Transient gynecomastia
- Alteration in other hormones secretion
- Increased growth and pigmentation of nevi
- Sleep apnea
- Pancreatitis

Overall 3% of treated children !!!
Indications for GH therapy

- GH deficiency
  - Idiopathic
    - Isolated
    - CPHD
  - Organic
    - Craniopharyngioma
    - Post surgery
    - Post irradiation

- Small for gestational age (SGA)
- Idiopathic short stature (ISS)
- Chronic kidney disease (CKD) and postrenal transplantation
- Turner syndrome
- Prader-Willi syndrome
- Noonan syndrome
Evaluation and monitoring adverse effects distinctive to the various indications for GH therapy
GH Deficiency

A **slightly high** risk of developing

- Headache and idiopathic intracranial hypertension $^{1,2}$
  - Craniopharyngiomas
  - Congenital GHD deficiency
  - Cranial tumors
- Increased intraocular pressure$^3$
- Alternation in other hormones metabolism

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$^1$ Critical evaluation of the safety of rGH administration: Statement from the GH Research Society. J Clin Endocrinol Metab, 2001
GH Deficiency

Monitoring

- Growth parameters including IGF-I levels
- Bone age
- Pubertal stage

- In children with isolated GHD and:
  - Abnormality on MRI of the H-P region
  - Following irradiation
  - Genetic mutations associated with evolving hypopituitarism

Regular evaluation of the hypothalamic-pituitary-adrenal and – thyroid* axes

*FT4 should be measured because the hypothyroidism is central
Small for gestational age (SGA)

- No specific short-term adverse effects during GH treatment as compared with other groups of GH treated children

- Concerns:
  - Insulin resistance
  - Adverse changes in blood pressure (higher baseline systolic BP) and lipid profiles

- Follow-up outcome:
  - Mild and reversible decreases in insulin sensitivity during treatment, without impaired glucose tolerance or T2DM
  - Normalization of the BP
  - Mean values for serum lipids and the atherogenic index
    - Normal at baseline
    - Decreased during growth hormone treatment

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2 de Zegher F et al. J Clin Endocrinol Metab, 2002
3 Cutfield WS et al. The US trial and KIGS analysis. Horm Res 2006
4 Sas T et al. J Clin Endocrinol Metab, 2000
Small for gestational age (SGA)

Monitoring

- Growth parameters including IGF-I levels
- Pubertal stage
- Bone age

- Metabolic parameters
  - Fasting insulin and glucose levels
  - HbA1c levels
Idiopathic short stature (ISS)

- The adverse effects of GH therapy in ISS are similar to or less than those seen in GH deficiency \(^1-^4\)

- Carbohydrate metabolism
  - Standard doses of GH have no adverse effect on blood glucose levels
  - Excessive doses of GH (≥0.3 mg/kg/week) induce a dose dependent increase in mean fasting and stimulated insulin levels
    Post-treatment - insulin sensitivity returned to normal

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\(^1\) Quigley CA et al. J Clin Endocrinol Metab 2005
\(^2\) Kemp SF et al. J Clin Endocrinol Metab 2005
\(^3\) Noto R et al. The Genentech National Cooperative Growth Study. J Pediatr Endocrinol Metab 2011
Idiopathic short stature (ISS)

Monitoring

- Growth parameters including IGF-I levels
  - The risks of giving excessive doses of exogenous GH may be reduced by using IGF-I targeted dosing strategies

- Bone age

- Pubertal stage
Chronic kidney disease (CKD)

- The overall number of adverse events in GH treated CKD patients is small; adverse effects are comparable in GH treated and untreated CKD patients\(^1\)

- There may be a slightly higher risk of developing
  - Idiopathic intracranial hypertension (pseudotumor cerebri)
  - Slipped capital femoral epiphysis
  - Worsening of existing scoliosis

- **No differences** in the risk of
  - Lipid profile abnormalities
  - Glucose intolerance and diabetes mellitus
  - Deterioration of renal osteodystrophy

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\(^1\) Fine RN *et al.* *Pediatr Nephrol* 2005
Chronic kidney disease (CKD)

Renal function

- In patients with CKD No difference in the risk of kidney function deterioration between GH treated and untreated CKD patients
  - Loss of residual renal function in CKD stages 2 to 4 was not accelerated in GH treated CKD children \(^1,^2\)

- In patients with CKD during dialysis or in **allograft recipients** treated with GH post-transplant
  - No effect on development of acute graft rejection \(^3,^4\)
  - No increased risk of post-transplant lymphoproliferative disease \(^5\)
  - No increase in the incidence of deterioration of renal function (NAPRTCS study) \(^3\)

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Chronic kidney disease (CKD)

Monitoring

- Growth parameters and pubertal stage
- Renal function (serum creatinine) and PTH
  - GH therapy should be reconsidered if there is
    - An unexplained decrease in renal function
    - Secondary hyperparathyroidism which may lead to bone deformities
- Glucose homeostasis (in patients with additional risk factors)
  - Concomitant glucocorticoid treatment
  - Familial T2DM
- Funduscopic examination (intracranial hypertension)
- Pelvic X-ray prior to initiating GH and to repeated studies if symptoms of SCFE occur
Turner syndrome

- Patients with TS appear to be at increased risk for adverse effects compared with other GH treated populations\(^1\)

- Adverse events associated with GH therapy
  - Idiopathic intracranial hypertension (pseudotumor cerebri)
  - Scoliosis
  - Slipped capital femoral epiphysis
  - Pancreatitis

\(^1\) Bolar K et al. The National Cooperative Growth Study. J Clin Endocrinol Metab 2008
Turner syndrome

- Carbohydrate metabolism and GH treatment
  - Insulin levels increase significantly during therapy compared to baseline
  - No glucose intolerance was detected during treatment
  - Insulin levels return to normal levels after the completion of therapy

- The cardiovascular system and GH treatment
  - No AE on blood pressure
  - Normal left ventricular morphology and function
  - No AE on left ventricular heart dimensions
  - No deleterious effects on aortic diameter or compliance

- Skin and GH treatment
  - No change in the number of nevi
  - Absence of malignant transformation of melanocytic nevi
  - No increased risk of skin neoplasia
Turner syndrome

Monitoring

- Growth parameters including IGF-I levels

- Orthopedic evaluation before initiating and throughout GH therapy for
  - Development or worsening of preexisting scoliosis
  - Early detection of epiphysiolysis due to increased risk of SCFE

- Cardiologic evaluation
- Dermatologic evaluation – nevi
- Glucose homeostasis including HbA1c levels
- Thyroid function tests
Prader-Willi syndrome (PWS)

- A genetic condition
  - Lack of expression of the paternally imprinted chromosome 15q11-q13

- Clinical characteristics (OMIM #176270)
  - 3H - hypotonia, hyperphagia, hypogonadism
  - **Short stature and scoliosis**
  - Psychomotor delay, and behavioral abnormalities

- Mortality rates are high
  - In infants and children: sudden death and respiratory illness
  - Adults: obesity and its complications
    - Type 2 diabetes mellitus
    - Hypertension
    - Sleep apnea
    - Cardiovascular disease
Prader-Willi syndrome (PWS)

Efficacy of GH treatment

- Improves height
- Body composition
  - Increased lean mass
  - Decreased fat mass
  - Improves the metabolic pattern of body fat distribution

C/I for GH treatment

- Morbid obesity (>225 percent of ideal body weight)
- Uncontrolled diabetes
- Untreated severe obstructive sleep apnea (adenotonsillectomy prior to GH therapy)
- Psychosis
Prader-Willi syndrome (PWS)

Pretreatment evaluation

- Obesity and its complication
- Glucose tolerance
- Upper airway obstruction or apnea including polysomnography
- Evidence of scoliosis
- Evidence of intracranial hypertension
Prader-Willi syndrome (PWS)

Adverse effects

- A coincidence of ~20 deaths in GH treated children with PWS\(^1\)
- Most occurred within the first 3 months of GH treatment
- The patients had one or more of the following risk factors\(^2\):
  - Severe obesity
  - Sleep apnea
  - Respiratory infection

- Most children do not experience these adverse effects\(^3\)
- GH treatment improves central hypoventilation and thereby\(^4\)
  - Improves sleep-disordered breathing
  - Improves pulmonary function

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\(^2\) Lee PDK. Growth, Genetics and Hormones journal 2013

\(^3\) Al-Saleh S et al. J Pediatr 2013

\(^4\) Miller J et al. J Clin Endocrinol Metab 2006
Prader-Willi syndrome (PWS)

Adverse effects

- Carbohydrate and lipids metabolism and GH treatment
  - No adverse effects in glucose homeostasis
  - No adverse effects on lipid profile

- Orthopedic problems and GH treatment
  - No increase in the risk or severity of scoliosis
  - No increase in the risk or severity of SCFE
Prader-Willi syndrome (PWS)

Monitoring

- Obstructive respiratory symptoms
  - Polysomnography
    - In patients with significant abnormalities prior to GH treatment - one month after beginning of treatment
    - In all patients who develop increased obstructive symptoms
  - Clinical evaluation
    - In all patients if they develop inter-current upper respiratory tract infections
  - Monitoring oxygen saturation during sleep
    - In hypotonic infants and toddlers for the first one to two months after starting GH treatment

- Glucose homeostasis
- Thyroid functions

## Routine safety monitoring for GH and non-GH deficient children

<table>
<thead>
<tr>
<th>Condition</th>
<th>Clinical assessment</th>
<th>Blood tests</th>
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<tbody>
<tr>
<td>GHD</td>
<td></td>
<td>Thyroid and adrenal functions</td>
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<tr>
<td>ISS</td>
<td></td>
<td>No special testing</td>
</tr>
<tr>
<td>SGA</td>
<td></td>
<td>HbA1c</td>
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<tr>
<td>CKD</td>
<td>SCFE</td>
<td>Renal function test ;PTH</td>
</tr>
<tr>
<td>Turner syndrome</td>
<td>Scoliosis</td>
<td>HbA1c, thyroid functions</td>
</tr>
<tr>
<td>PW syndrome</td>
<td>Sleep apnea</td>
<td>HbA1c, thyroid functions</td>
</tr>
</tbody>
</table>
GH treatment and malignancy

- Both GH and IGF-I have mitogenic and anti-apoptotic properties
- High-normal levels of IGF-I may increase rates of breast, prostate and colo-rectal cancers

- A concern: GH treatment might induce tumoro-genesis
  - Recurrence of a previously treated tumor
  - Induction of a second neoplasm
  - Appearance of a de-novo malignancy
GH treatment and malignancy – surveillance studies

- **The Childhood Cancer Survival Study (CCSS)**\(^1\)
  In the cohort of 361 patients treated with GH, the relative risk of developing a second neoplasm, **mostly meningioma**, was 2.15 (95% CI, 1.33-3.47)
  (It is still unclear whether the incidence of meningiomas might be increased in patients with GHD secondary to cranial irradiation)

- **National Cooperative Growth Study (NCGS), Genentech**\(^2\):
  In 54,996 GH treated children (1985 -2006) no GH-associated increased risk of any new malignancies in GHD and non-GHD patients

- **KIGS—the Pfizer International Growth Database**\(^3\):
  No increased incidence of cancer in 58,603 GH treated patients without prior cancer or risk factors for developing cancer relative to the normal population

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\(^1\)Sklar CA et al. J Clin Endocrinol Metab 2002
\(^2\)Bell J et al. J Clin Endocrinol Metab 2010
\(^3\)Wilton P et al. J Pediatr 2010
Long-Term Safety of Recombinant Human Growth Hormone in Children

J. Bell, K. L. Parker, R. D. Swinford, A. R. Hoffman, T. Maneatis, and B. Lippe

<table>
<thead>
<tr>
<th>TABLE 1. Incidence of targeted events by indication</th>
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<tr>
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<tr>
<td>n</td>
</tr>
<tr>
<td>AE</td>
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<tr>
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<tr>
<td>Deaths</td>
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<tr>
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</tr>
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<td>Pancreatitis</td>
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</tbody>
</table>

Data are expressed as percentage. IGHD, Idiopathic GHD; IC, intracranial.

* New onset, no risk factors.
* Based on fewer than 15 reports.
GH treatment and malignancy – surveillance studies

Risk of Neoplasia in Pediatric Patients Receiving Growth Hormone Therapy—A Report From the Pediatric Endocrine Society Drug and Therapeutics Committee / A PubMed search conducted through February 2014

- Children **without prior cancer** or known **risk factors for developing cancer**:
  - No association between GH therapy during childhood and neoplasia

- **Pediatric cancer survivors** who are in remission:
  - GH does not increase the risk of recurrence
  - GH may increase the risk for subsequent primary neoplasms

- Patients who are at higher risk for developing cancer should be critically analyzed on an individual basis, and if chosen, appropriate surveillance for malignancies should be undertaken.

*Raman et al. J Clin Endocrinol Metab 2015*
Potential long-term adverse effects of GH therapy

- Cardiovascular disease
- Development of neoplasms
The Safety and Appropriateness of Growth hormone treatments in Europe (SAGhE) study

A multinational European epidemiological study

**Aim:** Long-term safety of GH treatment in young adults with "low-risk" conditions (short stature associated with GHD, ISS, or SGA) who initiated treatment during childhood (between 1985 and 1997)

- **Results of the French study (2010-2012)**
  - Modestly higher mortality rate in GH-treated vs. controls
    - [SMR (standardized mortality ratio) 1.33 (95% CI, 1.08-1.64)]
  - Cardiovascular disease - responsible for most of the excess mortality
  - Bone tumor-related mortality was increased
    - [SMR 5.00 (95% CI, 1.01–14.63)]

- **Results of the study from Belgium, the Netherlands & Sweden**
  - No long-term risks attributable to GH treatment

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The Safety and Appropriateness of Growth hormone treatments in Europe (SAGhE) study

- FDA and EMA\(^1\)
  - The weaknesses in the French study's design render it inconclusive
  - No change in the prescription of GH should be made before SAGhE study is concluded and new long-term surveillance studies are conducted

GH treatment and hemorrhagic stroke

- French SAGhE group - a second study
  - Increased risk of hemorrhagic stroke in adults who were treated with GH in childhood

- Expert review from the Endocrine Society, Pediatric Endocrine Society, and Growth Hormone Research Society
  - Important deficiencies in the study's methods that warrant skepticism about its conclusions
  - This study does not provide sufficient evidence to change prescribing practices or warrant increased surveillance for stroke in adults who were treated with GH during childhood

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1 Povidin A et al. Neurology 2014; 83:780
2 https://www.endocrine.org....Accessed on September 08, 2014
Potential long-term adverse effects of GH therapy

SAGhE group:

Definitive answers await analysis of the full cohort of approximately 30,000 children/adolescents who were treated with human GH and evaluated decades later.
Unmet expectations
ISS response to GH treatment
Summary

- Treatment with GH has been approved for GHD and a number of other non-GH deficient patients with growth impairment.

- In each one, it has been shown that GH therapy is efficient in increasing growth velocity and final height.

- Mild side effects are not unusual, although they are frequently transient and tolerable.

- In contrast, serious adverse events that require discontinuation of the medication are rare, but need to be continuously monitored throughout the treatment.

- Further epidemiological studies are required to establish the long-term safety of GH therapy in adults who were on treatment during childhood.
Thank you
Association between growth hormone therapy and mortality, cancer and cardiovascular risk: Systematic review and meta-analysis

Annalisa Deodati a, Barbara Baldini Ferroli a, Stefano Cianfarani a,b,*

Design: A systematic review of all articles published until September 2013 was carried out.

The primary efficacy outcome measures were the all-cause, cancer and cardiovascular standardized mortality ratios (SMR).

The secondary efficacy outcome measures were the standardized incidence ratio (SIR) for cancer and the relative risk (RR) for second neoplasms.

Results: The overall all-cause SMR was 1.19 (95% CI 1.08–1.32, p < 0.001).

Malignancy and cardiovascular SMRs were not significantly increased.

Both the overall cancer SIR 2.74 (95% CI 1.18–5.41), and RR for second neoplasms 1.99 (95% CI 1.28–3.08, p = 0.002), were significantly increased.

Conclusions: The results of this meta-analysis may raise concern on the long-term safety of GH treatment. However, several confounders and biases may affect the analysis.

Independent, longterm, well-designed studies are needed to properly address the issue of GH therapy safety.