# “To Treat or Not To Treat GHD in Adults” is the question

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# Agenda

- Clinical features of GHD in adults
- Evaluate the evidence for the benefits of rhGH replacement
- Challenges with rhGH therapy in adults with GHD
- Overview of current recommendations regarding the management of GHD in adults

**Patient:** 38-year-old woman (BMI: 22kg/$m^2$)

**History:**
NFPAs/ Trans-Sphenoidal Surgery and Radiotherapy 2 years ago
On stable replacement for cortisol, thyroid, and sex hormones

**Symptoms:**
Profound fatigue, "can't lose weight," depressed mood
AGHDA score: 18/25

**Labs:**
IGF-1: 65 ng/mL (low for age-sex)
Failed Glucagon Stimulation Test (Peak GH: 0.4 ng/mL)

**Patient:** 48-year-old obese male (BMI 34 kg/$m^2$)

**History:**
Resistant prolactinoma who underwent TSS
He is on hormone replacement therapy with prednisolone and testosterone.

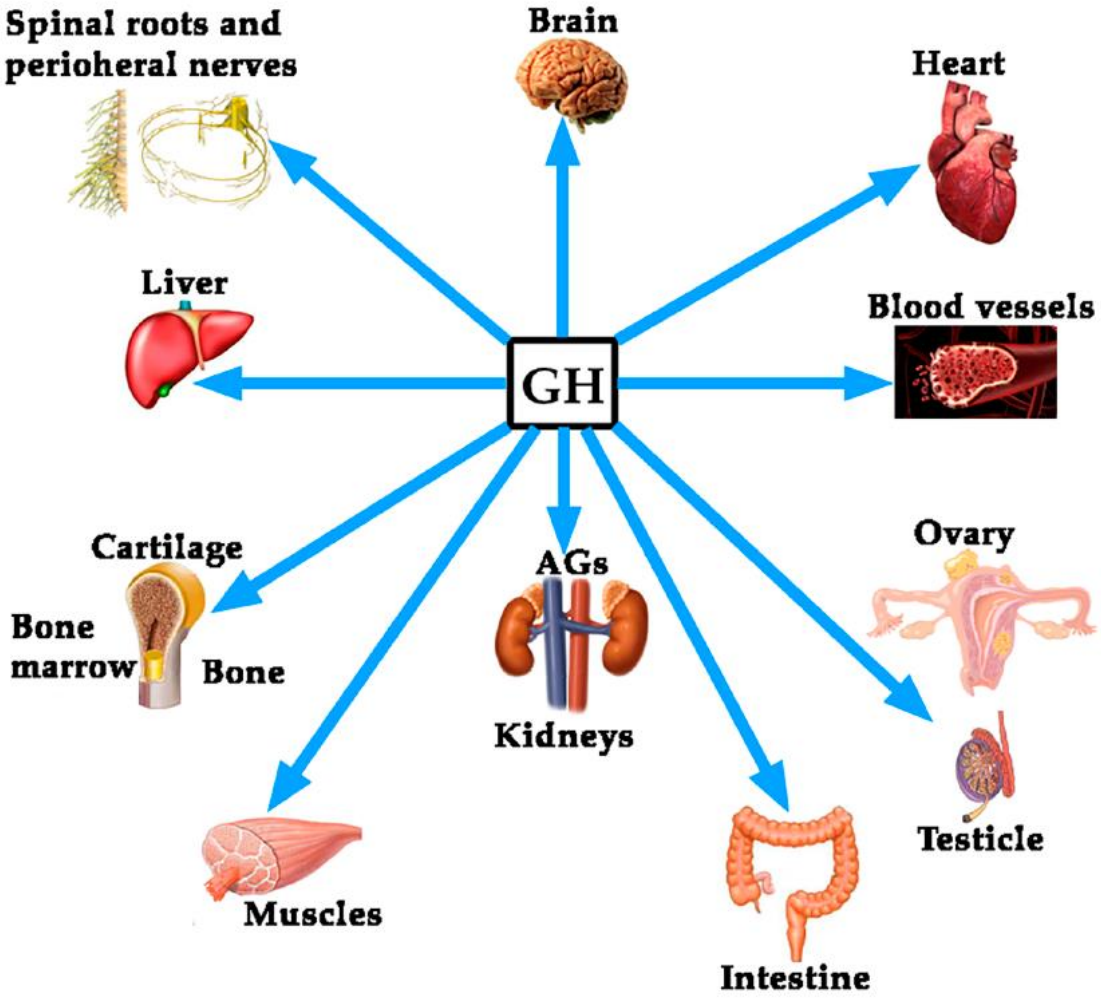
**Symptoms:**
Fatigue, poor exercise tolerance
AGHDA score: 10/25

**Labs:**
IGF-1: 80 ng/mL (low for age-sex)
Glucagon Stimulation Test: Peak GH 1.1 ng/mL (equivocal)
Testosterone :0.6 ng/ml

**GHD is Not just a lab value, but a syndrome with multi-systemic consequences.**

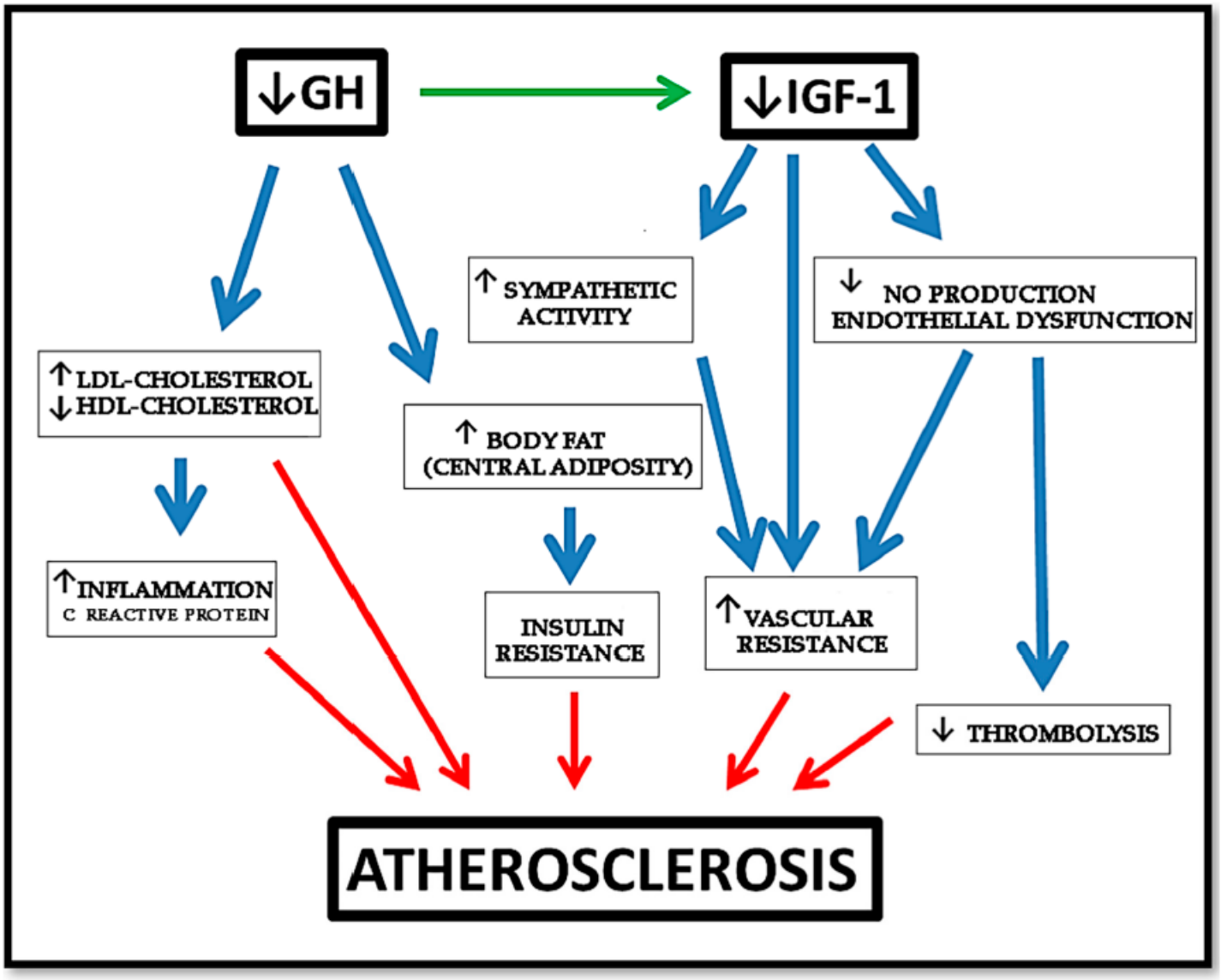
**Body composition** **Quality of Life** **Cardiac function**

**Bone**




Int. J. Mol. Sci. 2018, 19, 290

# Effects of GH deficiency on Cardiovascular and metabolism




Int. J. Mol. Sci. 2018, 19, 290

# Evidence for the benefits of rhGH replacement

Change in **body composition** and **lipids** from baseline among GH-treated and placebo patients

Meta-analysis of 22 RCT
Duration of F/U: 6mo

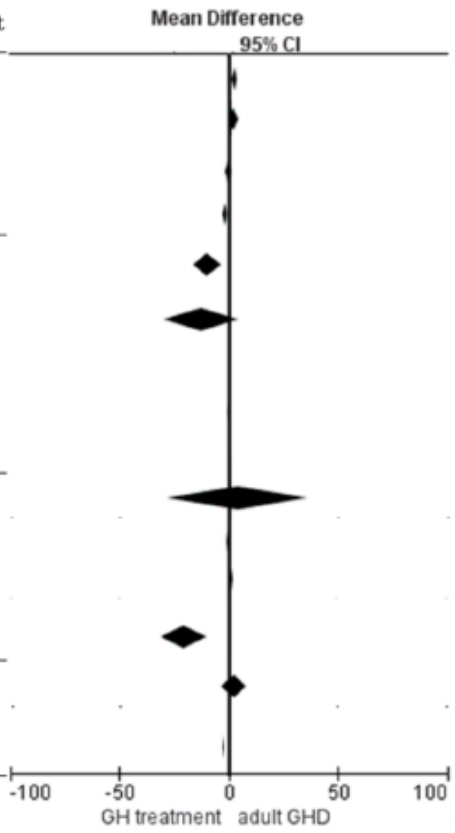
| Parameter | GH-treated | Placebo | |
|---|---|---|---|
| | Weighted mean ± SD (n*) | Weighted mean ± SD (n*) | *P* value** |
| Body weight (kg) | −0.49 ± 7.02 (9) | 0.38 ± 6.58 (9) | 0.1 |
| Body mass index (kg/m$^2$) | −0.18 ± 2.86 (7) | 0.09 ± 2.09 (6) | 0.2 |
| Lean body mass (kg) | 2.61 ± 6.79 (18) | 0.04 ± 4.53 (14) | <0.0001 |
| Fat mass (kg) | −2.19 ± 13.52 (14) | 0.31 ± 6.80 (11) | 0.0002 |
| $VO_2$ Max (L/min) | 0.93 ± 6.48 (7) | 0.24 ± 1.40 (7) | 0.2 |
| Total Cholesterol (mmol/L)[a] | −0.38 ± 1.14 (14) | 0.01 ± 0.88 (13) | <0.0001 |
| LDL Cholesterol (mmol/L)[a] | −0.42 ± 1.80 (11) | −0.10 ± 1.62 (10) | 0.0009 |
| HDL Cholesterol (mmol/L) | 0.14 ± 0.56 (10) | 0.05 ± 0.79 (9) | 0.09 |
| Triglycerides (mmol/L)[a] | 0.02 ± 0.80 (13) | −0.02 ± 2.12 (12) | 0.7 |
| IGF-1 (nmol/L) | 21.23 ± 36.98 (18) | 0.36 ± 5.71 (14) | <0.0001 |

Pituitary 2015, 18, 297–305

Meta-analysis of 11 studies on **cardiovascular effect** of GH replacement in adults with GHD

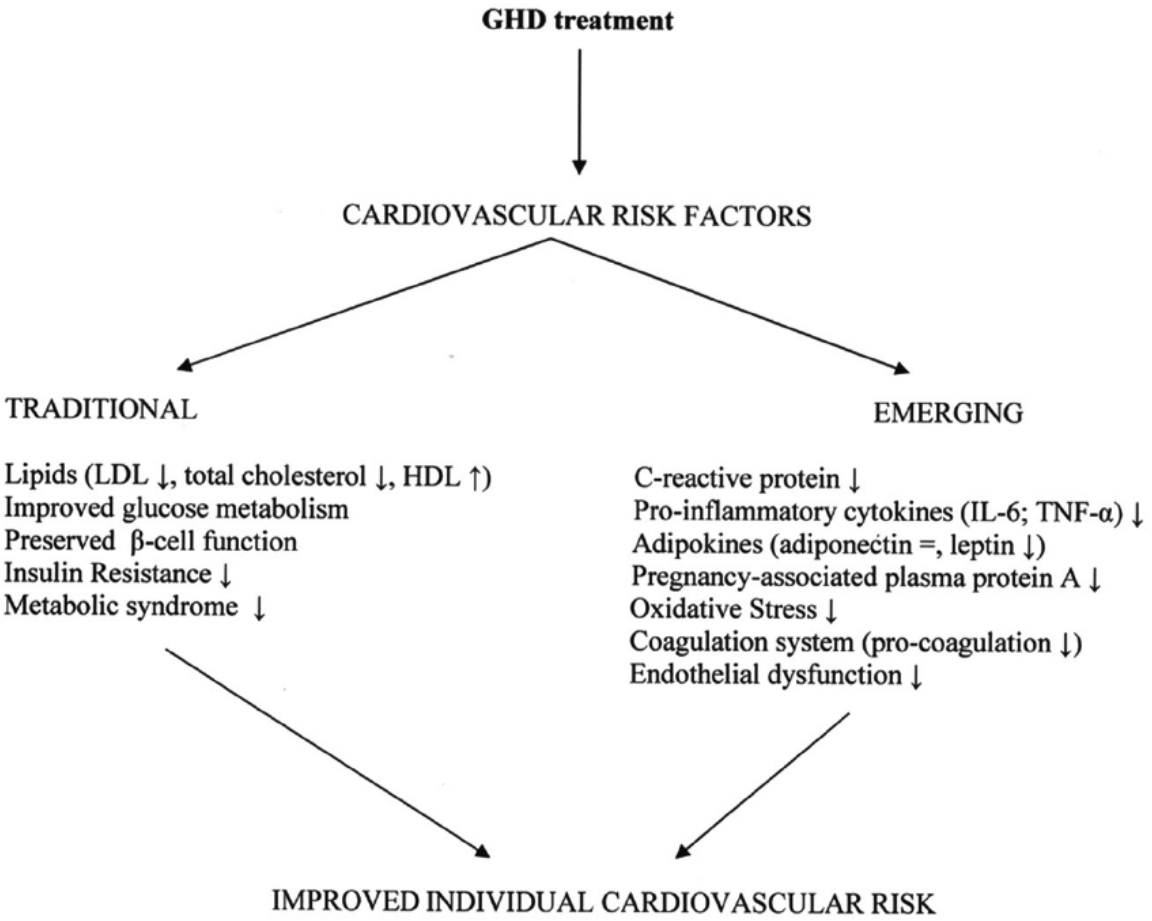
Duration of follow-up:6-12 mo

| | | No. of Trials | No. of patients: GH treatment | No. of patients: adult GHD | Q Test ($p$) | effect model | Mean Difference, 95% CI | effect |
|---|---|---|---|---|---|---|---|---|
| General indicators | BHR (bpm) | 3 | 54 | 56 | NS | Fixed | 3.03[2.00, 4.06] | ↑ |
| | PHR (bpm) | 3 | 57 | 57 | NS | Fixed | 2.04[-0.3, 4.38] | — |
| | SBP (mmHg) | 6 | 391 | 391 | NS | Fixed | -0.39[-0.96, 1.74] | — |
| | DBP (mmHg) | 7 | 405 | 405 | NS | Fixed | -1.19[-2.33, -0.05] | ↓ |
| Indicators of cardiac structure | LVEDV (ml) | 3 | 90 | 90 | NS | Fixed | -9.84[-16.53, -3.15] | ↓ |
| | LVESV (ml) | 3 | 62 | 73 | $p<0.05$ | Random | -12.42[-29.89, 5.04] | — |
| | LVIS (mm) | 4 | 130 | 130 | NS | Fixed | 0.50[0.43, 0.57] | ↑ |
| | LVM (g) | 4 | 102 | 102 | NS | Fixed | 0.35[-0.17, 0.87] | — |
| | LVPW (mm) | 4 | 175 | 175 | NS | Fixed | 0.50[0.43, 0.57] | ↑ |
| Indicators of cardiovascular function | DT (ms) | 3 | 121 | 121 | $p<0.05$ | Random | 3.89[-27.98, 35.76] | — |
| | E/A | 4 | 102 | 102 | NS | Fixed | -0.00[-0.03, 0.03] | — |
| | EF (%) | 6 | 130 | 130 | NS | Fixed | 2.12[1.34, 2.90] | ↑ |
| | NT-BNP (pg/ml) | 4 | 71 | 84 | NS | Fixed | -206.34[-308.95, -103.72] | ↓ |
| Indicators of life quality | Peak $VO_2$ (ml/kg/min) | 3 | 62 | 73 | $p<0.05$ | Random | 2.33[-3.07, 7.73] | — |
| | $VE/VCO_2$ slope | 3 | 62 | 73 | NS | Fixed | -2.31[-2.92, -1.71] | ↓ |



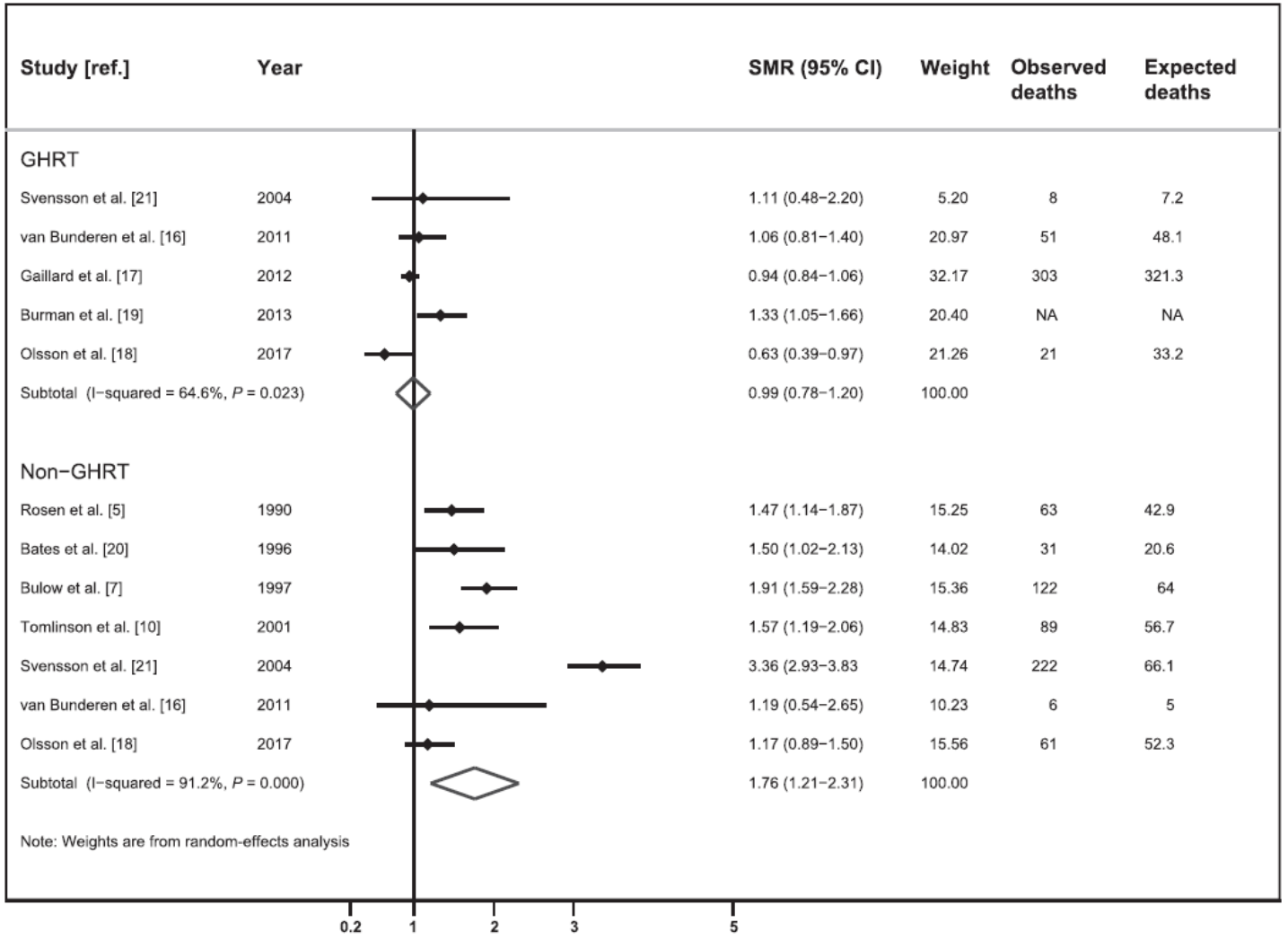

pituitary; Volume 23, pages 467–475, (2020)

# The potential impact of GH replacement on the individual **cardiovascular risk**




*J Clin Endocrinol Metab* 99: 18–29, 2014

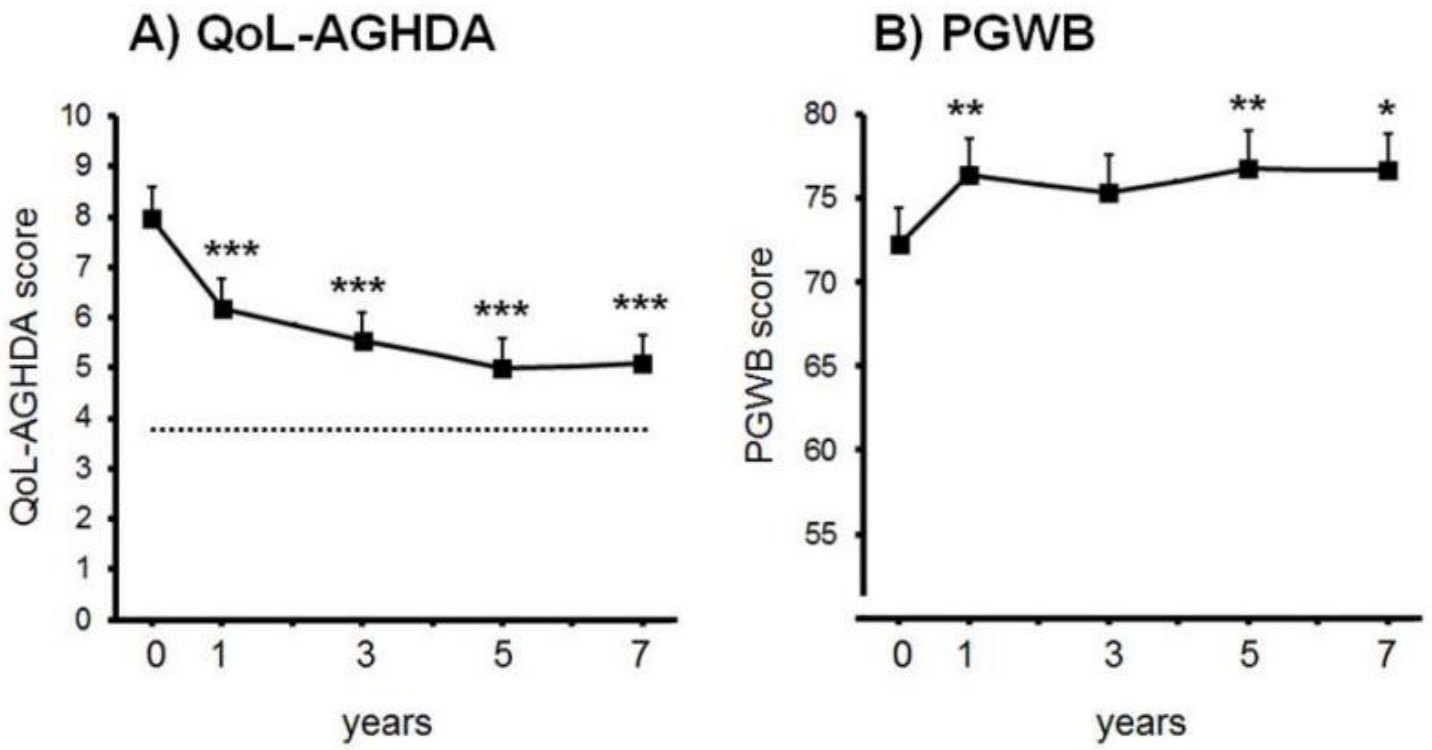
# Meta-analysis of studies investigating **mortality** in patients with hypopituitarism with and without GHRT




Best Practice & Research Clinical Endocrinology & Metabolism 37 (2023)

# Quality of life (QoL) in hypopituitary patients with adult onset GHD during 7 years of GH replacement

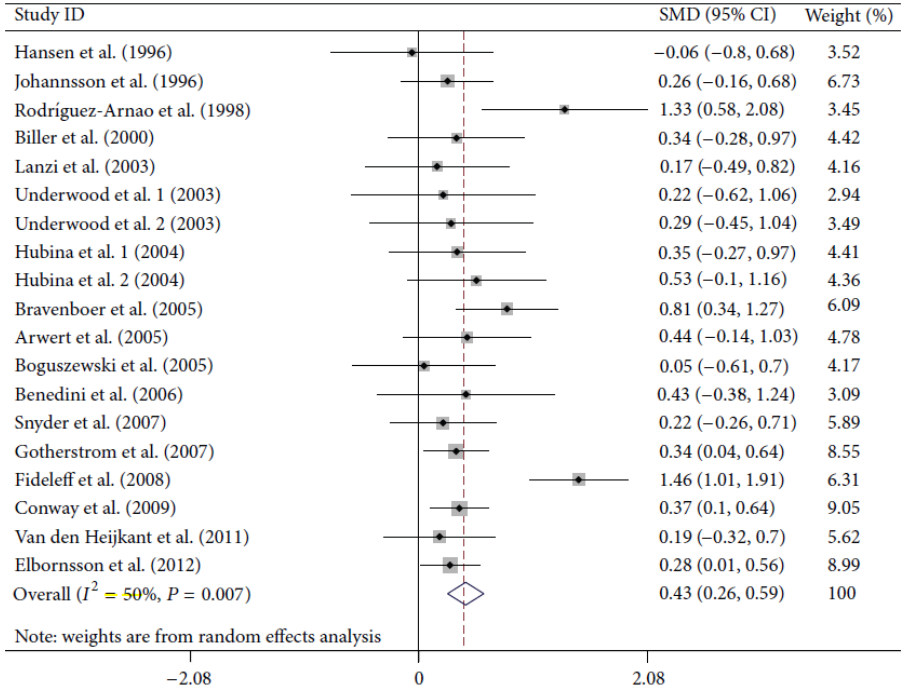
N=95

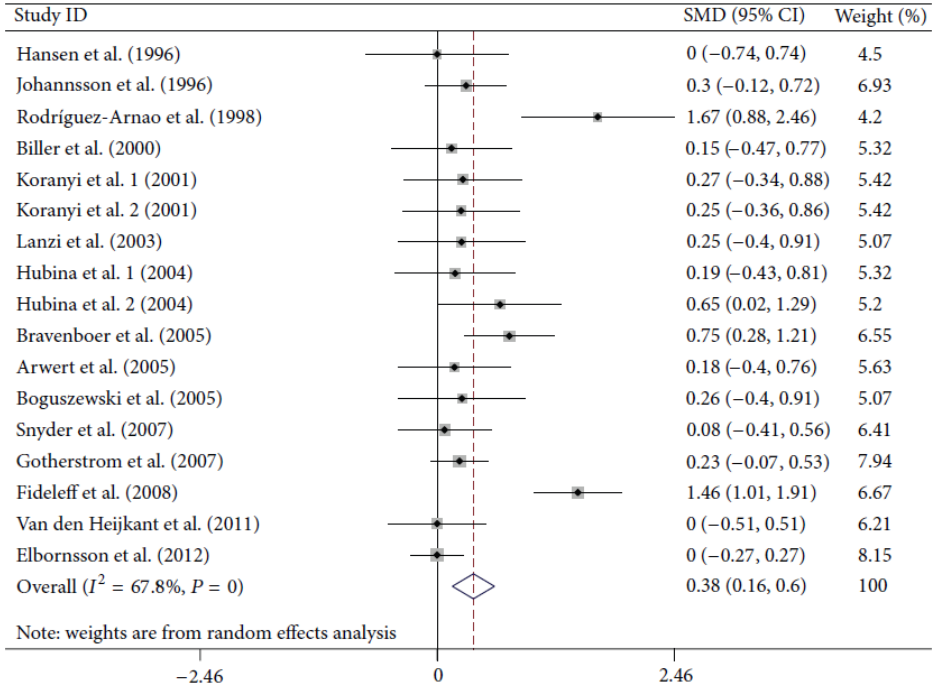



Eur. J. Endocrinol. 2017, 176, 99–109

# Forest plot for the association between GH treatment and **BMD** of spine and femoral neck

20 studies, 936 participants
Duration of F/U 1-15 yrs




Int. J. Endocrinol. 2013, 2013, 216107

# Relative risk for **neoplasm outcomes** in GH-treated vs untreated patients: using HypoCCS database

Mean follow-up:4.8 yrs

| Outcome measure | GH-treated *n*/*N* (%) | Untreated *n*/*N* (%) | Total *n*/*N* (%) | *P* value $\chi^{2a}$ | *P* value CMH[b] | Relative risk (95% CI)[c] |
|---|---|---|---|---|---|---|
| Primary malignancy[d] | 217/8410 (2.6) | 44/1265 (3.5) | 261/9675 (2.7) | 0.07 | 0.98 | 1.00 (0.70–1.41) |
| Pituitary adenoma recurrence[d] | 257/3537 (7.3) | 56/720 (7.8) | 313/4257 (7.4) | 0.63 | 0.53 | 0.91 (0.68–1.22) |
| Craniopharyngioma recurrence | 64/956 (6.7) | 5/102 (4.9) | 69/1058 (6.5) | 0.49 | 0.55 | 1.32 (0.53–3.31) |

Eur. J. Endocrinol. 2015, 172,779–790

| Patient data | Benefits | Risks |
|---|---|---|
| Body composition | Reduction in fat mass<br>Increase in lean mass | Increase in BMI<br>Increased waist circumference |
| Cardiovascular risk markers | Increase in HDL-chol<br>Reduction of total and LDL-chol<br>Diastolic blood pressure reduction<br>Reduction of CRP<br>Reduction of carotid intima-media thickness | Reduced insulin sensitivity<br>Increase in fasting glucose and insulin<br>Trend to the increase in the prevalence of metabolic syndrome<br>Increase in lipoprotein (a) |
| Mortality | Tendency to decrease the global mortality of hypopituitarism | Persistence of higher mortality than the general population in some studies |
| Health-related quality of life | Improvement in quality of life questionnaires<br>Greater benefit in patients with low quality of life at baseline | No improvement in all dimensions<br>Probable absence of effect in patients with normal quality of life |
| Bone metabolism | Increase in bone mineral density | Effect on the incidence of fractures not clearly shown |
| Neoplasms | No increase in the rate of recurrence or progression of hypothalamic-pituitary tumors<br>No increase in overall risk of neoplasia in adults with GHD | Tendency to increase risk of second malignancy in childhood cancer survivors treated with GH in childhood |

Int. J. Mol. Sci. 2018, 19, 893

# Challenges with rhGH therapy in adults with GHD

## Overview of current recommendations

# The Diagnostic Challenge:

**Whom to Test:**

- Patients with known pituitary disease
- History of traumatic brain injury, subarachnoid hemorrhage (12 months following the events)
- Childhood GHD requiring retesting

**Initial Work-up:** Low age-sex-matched IGF-1

**Dynamic Stimulation Tests:**

- Insulin Tolerance Test (ITT) - gold standard but risky
- Glucagon Stimulation Test (GST)

GHD Clinical Practice Guidelines, *Endocr Pract.* 2019;25(No. 11)

## In whom Dynamic Stimulation Tests are not necessary:

- Patients with organic hypothalamic-pituitary disease (e.g., suprasellar mass with previous surgery and cranial irradiation) who have **MPHD (≥3 PHD)** and **low sex-age matched IGF-1**

- Patients with **genetic defects** affecting the hypothalamic-pituitary axes

GHD Clinical Practice Guidelines, *Endocr Pract.* 2019;25(No. 11)

## Considerations before GH–stimulation tests :

GH–stimulation tests should only be performed after **all other Pituitary hormone deficiency** have been **optimally replaced with stable hormone replacement dose.**

In patients with **isolated GHD:** 2 tests recommended

GHD Clinical Practice Guidelines, *Endocr Pract.* 2019;25(No. 11)

- **ITT** remains the gold-standard test to establish the diagnosis of **adult GHD using a peak GH cut-point of 5 µg/L** (ng/ml)

- This test is increasingly **used less frequently** because of **safety concerns**, potential to cause severe hypoglycemia

- **Contraindicated** in certain patients, such as **elderly patients** and those with **seizure disorders** and **cardio/cerebrovascular disease.**

- **GST** could be considered as the alternative test

GHD Clinical Practice Guidelines, *Endocr Pract.* 2019;25(No. 11)

- **For the GST**, we recommend **utilizing BMI-appropriate GH cut-points** to diagnose adult GHD **to reduce the possibility of misclassifying GH-sufficient patients** because **increased BMI is associated with decreased glucagon-induced GH stimulatory effect.**
- normal-weight (**BMI <25 kg/m$^2$**) and overweight (**BMI 25 to 30 kg/m$^2$**) patients with a **high pretest probability**:

  GH cut-point of **3 µg/L**

- obese (**BMI >30 kg/m$^2$**) and overweight (**BMI 25 to 30 kg/m$^2$**) patients with a **low pretest probability**:

  GH cut-point of **1 µg/L**

- In patients with **glucose intolerance**, the **diagnostic accuracy of the GST remains unclear**

GHD Clinical Practice Guidelines, *Endocr Pract.* 2019;25(No. 11)

## Initiation and titration of rhGH: Start Low Go Slow

Low rhGH dosages **(0.1 to 0.2 mg/day)** in GH-deficient patients with concurrent:

- DM, previous gestational DM
- obesity
- older age

Higher rhGH starting doses **(0.3 to 0.4 mg/day)** in:

- young adults <30 years of age
- women on oral estrogen therapy

GHD Clinical Practice Guidelines, *Endocr Pract.* 2019;25(No. 11)

- Initially, follow patients at **1- to 2-month intervals**
- Increase the rhGH dose in increments of **0.1 to 0.2 mg/day** based on:

  **clinical response**

  **serum IGF-1 levels** (within the age-sex adjusted reference range )

  **side effects:**

  Arthralgias, Myalgias, edema, carpal tunnel syndrome, insulin resistance

  increase in ICP

- Once **maintenance doses** are achieved, follow-up can be implemented at approximately **6- to 12-month intervals**.

- **Shorter follow-up time intervals** and **smaller dose increments** can be implemented especially for the **elderl**y, and those with other comorbidities, such as **DM**

GHD Clinical Practice Guidelines, *Endocr Pract.* 2019;25(No. 11)

The following **parameters** may be assessed at approximately 6- to 12-month intervals:

- serum IGF-1
- fasting glucose, hemoglobin A1c, fasting lipids
- BMI, waist circumference, waist-to-hip ratio
- serum-free T4
- HPA axis via early morning cortisol or cosyntropin stimulation test
- **baseline MRI** in patients with any **post-surgical tumor remnant in the hypothalamic-pituitary region** before initiating rhGH, and **periodic MRIs** during rhGH therapy

GHD Clinical Practice Guidelines, *Endocr Pract.* 2019;25(No. 11)

The **optimal duration of rhGH replacement** therapy **remains unclear**.

If patients on rhGH replacement experience **beneficial effects** on QoL and objective improvements in biochemistry, body composition, and bone mineral density, rhGH treatment can be continued **indefinitely**

GHD Clinical Practice Guidelines, *Endocr Pract.* 2019;25(No. 11)

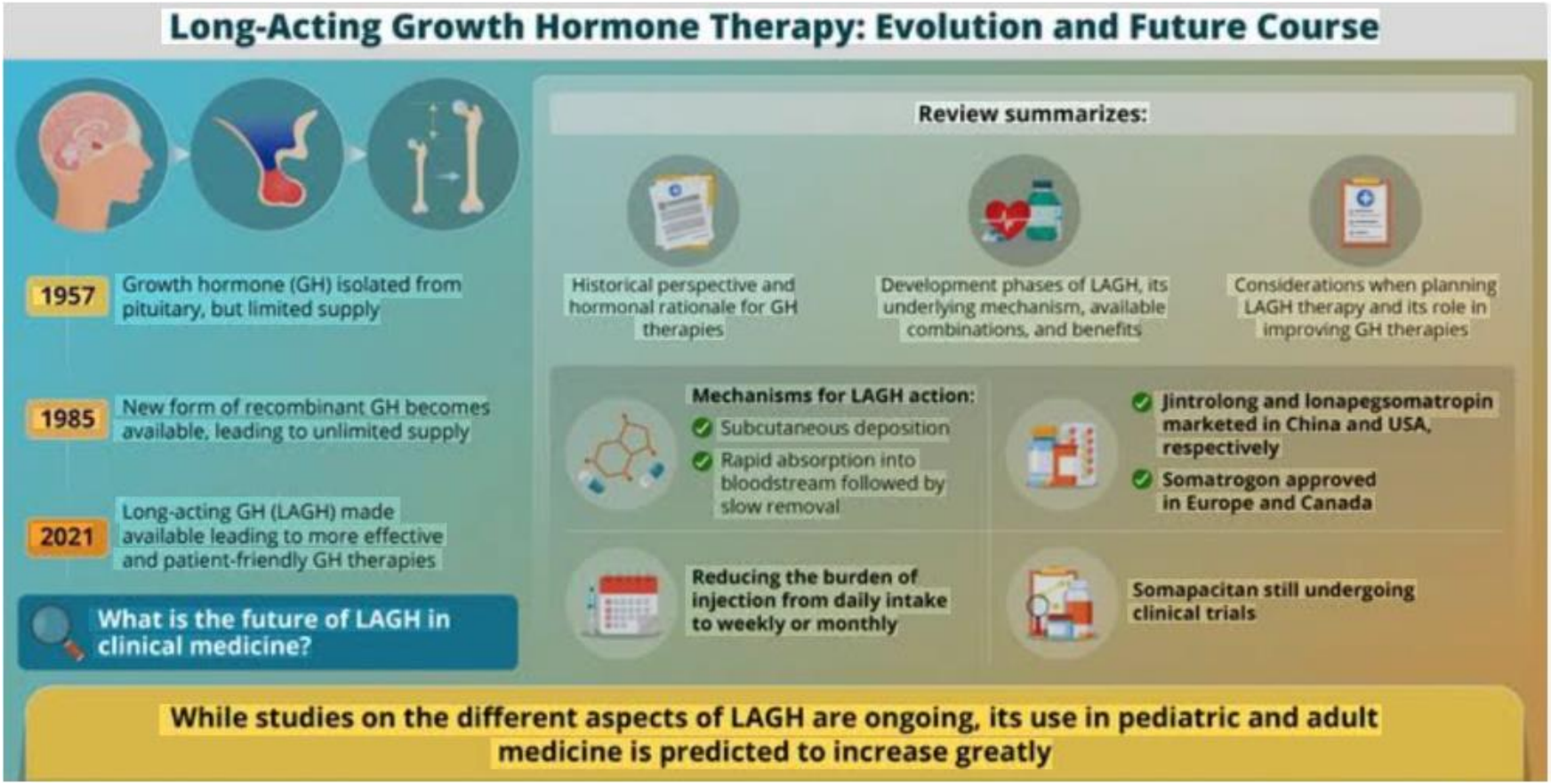
## rhGH is contraindicated in patients with a history of:

- active malignancy (other than basal-cell or squamous-cell skin cancers)
- active proliferative or severe non-proliferative diabetic retinopathy

Treatment with rhGH should be conducted **with caution** in patients with a **strong family history of cancer**

GHD Clinical Practice Guidelines, *Endocr Pract.* 2019;25(No. 11)

**weekly long-acting GH (LAGH)** preparations are currently **under development**



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**History:**
NFPAs/ Trans-Sphenoidal Surgery and Radiotherapy 2 years ago
On stable replacement for cortisol, thyroid, and sex hormones

**Symptoms:**
Profound fatigue, "can't lose weight," depressed mood
AGHDA score: 18/25

**Labs:**
IGF-1: 65 ng/mL (low for age-sex).
Failed Glucagon Stim Test (Peak GH: 0.4 ng/mL)

**Decision and Outcome:**
Started on low-dose GH
At 1 year, reports "life-changing" improvement in energy, lost 4% body fat
AGHDA score now 6

**Patient:** 48-year-old obese male (BMI 34 kg/$m^2$)

**History:**
Resistant prolactinoma who underwent TSS
He is on hormone replacement therapy with prednisolone and testosterone.

**Symptoms:**
Fatigue, poor exercise tolerance.
AGHDA score: 10/25.

**Labs:**
IGF-1: 80 ng/mL (low-normal for age-sex)
Glucagon Stim Test: Peak GH 1.1 ng/mL (equivocal)
Testosterone :0.6 ng/ml

**Decision and Outcome:**
After extensive discussion, decision was made **NOT to treat.**
Focus shifted to lifestyle intervention (diet, exercise) for weight loss and adequate testosterone replacement.
Energy improved with 10% weight loss.

# Take home message

A **low IGF-1** is a red flag, but it's **not diagnostic**.

The stimulation tests are **crucial**, but they are **not perfect**.

We must consider the clinical context **pre-test probability** to avoid misdiagnosis.

**<u>The Case FOR Treatment:</u>**

**Robust and Consistent Data Shows Improvement in:**

**Body Composition:** ↑ Lean mass, ↓ Fat mass.
**Bone Health:** ↑ BMD over 1-2 years.
**Lipid Profile:** ↓ LDL cholesterol.
**Quality of Life:** Significant improvements in validated questionnaires

**The Cancer Question:**

No conclusive evidence for increased *de novo* cancer risk, but caution in those with a history of malignancy.

**The Burden:**

**Cost:** Extremely high. One of the most expensive chronic therapies.

**Administration:** Daily subcutaneous injections.

**Monitoring:** Requires frequent follow-up and dose titration.

# To Treat or Not To Treat GHD in Adults?

**There is no one-size-fits-all answer.**

**We should balance <u>significant potential benefits</u> against <u>significant costs</u> and <u>risks.</u>**