Obtaining Proper Growth Hormone Lab Levels

And New Safety Information Regarding HGH – What HGH Research Has Taught Us...

BY DAN PURSER, MD
*POSSIBLE TEST QUESTIONS TODAY*
HOW TO OBTAIN A PROPER IGF-1?

Under what circumstances should you strive to get a proper IGF-1?

What really affects IGF-1 levels?

Drugs that affect IGF-1 levels?

Does exercise affect IGF-1 levels?

Does diet affect IGF-1 levels?

Does sexual activity affect IGF-1 levels?

Do other hormones affect IGF-1 levels?

Does IGF-1 level affect other hormone levels?
What is HGH?

Huge complex molecule.

Critical to sleep and body being able to heal.

Critical to mental well being too – maybe the most critical thing.

Something rarely, if ever, covered by insurance.
Is HGH safe to give?

Prospective safety surveillance of GH-deficient adults: comparison of GH-treated vs untreated patients.

Collaborators (173)
Author information
1Lilly Research Laboratories, Indianapolis, Indiana 46285, USA.

Abstract
CONTEXT: In clinical practice, the safety profile of GH replacement therapy for GH-deficient adults compared with no replacement therapy is unknown.

OBJECTIVE: The objective of this study was to compare adverse events (AEs) in GH-deficient adults who were GH-treated with those in GH-deficient adults who did not receive GH replacement.

DESIGN AND SETTING: This was a prospective observational study in the setting of US clinical practices.

PATIENTS AND OUTCOME MEASURES: AEs were compared between GH-treated (n = 1988) and untreated (n = 442) GH-deficient adults after adjusting for baseline group differences and controlling the false discovery rate. The standardized mortality ratio was calculated using US mortality rates.

RESULTS: After a mean follow-up of 2.3 years, there was no significant difference in rates of death, cancer, intracranial tumor growth or recurrence, diabetes, or cardiovascular events in GH-treated compared with untreated patients. The standardized mortality ratio was not increased in either group. Unexpected AEs (GH-treated vs untreated, P ≤ .05) included insomnia (6.4% vs 2.7%), dyspnea (4.2% vs 2.0%), anxiety (3.4% vs 0.9%), sleep apnea (3.3% vs 0.9%), and decreased libido (2.1% vs 0.2%). Some of these AEs were related to baseline risk factors (including obesity and cardiopulmonary disease), higher GH dose, or concomitant GH side effects.

CONCLUSIONS: In GH-deficient adults, there was no evidence for a GH treatment effect on death, cancer, intracranial tumor recurrence, diabetes, or cardiovascular events, although the follow-up period was of insufficient duration to be conclusive for these long-term events. The identification of unexpected GH-related AEs reinforces the fact that patient selection and GH dose titration are important to ensure safety of adult GH replacement.

PMID: 23345098 [PubMed - indexed for MEDLINE]  PMCID: PMC3677286  Free PMC Article
What does HGH do in an adult?

It is the **healing hormone** first and foremost.

**Helps with sleep** and somnolence — causes REM sleep.

**Helps clear brain fog.**

**Helps with fatigue.**

**Improves immune system functionality.**

**Gives mental stability** — prevents PTSD.
Where is **HGH** created?

In the upper portion of the anterior pituitary (front of the pituitary).

This area is most likely to be injured with a TBI.

Catches on the edge of the sella turcica.

LOC event? 100% chance of pituitary damage...
How is **HGH** released?

Upon signal from the hypothalamus.

**L-arginine** causes a big release.

Lowered blood sugar causes release (ITT).

**Stress** causes a release.

**Exercise** causes a release.
How does HGH react once released?

**GROWTH HORMONE**

- **GHRH** - Growth Hormone Releasing Hormone
- **GH** - Growth Hormone
- **IGF-1** - Insulin-like Growth Factor

- **Hypothalamus**
  - **GHRH**
  - **Somatostatin**

- **Pituitary gland**
  - **GH**
  - **Ghrelin**

- **Liver**
  - **IGF-1**

**Breaks up into 23 other hormones.**

This occurs in milliseconds.

Almost all of these, except one, are very short-lived.

The only one that hangs around for any amount of time is the IGF-1.

So we check IGF-1.
IGF-1 acts as a proxy measurement of HGH
Sub-hormones released from HGH when it is broken up?

IGF-1 & IGF-BP3
How do you obtain “proper” HGH levels?

Hard to do.

Must prepare the patient.

Must have the right tubes.

[GREEN TUBE FROZEN ON DRY ICE]

Potentially very inaccurate.

So instead we get an IGF-1 as the proxy.
Things that **FALSELY** elevate IGF-1 level?

- **Exercise** (intercourse IS exercise)
- **Certain medications**
- **Food** (so should be fasting – water is okay)
- **Grehlin** – containing food (beans, nuts, etc)
Medications that FALSELY elevate IGF-1 levels?

Provigil®
Nuvigil®
Effexor®
Zoloft®
Cymbalta®
Lyrica®

Hold for 24 hours IF possible or safe before drawing Fasting AM IGF-1.

In research we often held for 3 days to three weeks (usually a bad idea).
Foods that FALSELY elevate IGF-1 levels?

All foods will so they should “water fast 24-72 hours” before the blood draw (alright to drink pure water but nothing else).

Nuts (contain ghrelin). NO PEANUT BUTTER!

Any protein that contains l-arginine (which is most).

Fast for at least 24 hours IF possible or safe before drawing AM IGF-1. We often do 72 hours if in doubt.

Coffee is okay (no cream or sugar).
A “PROPERLY” obtained IGF-1

No stress the few days before.

No sex the day or night before.

“(Just) Water fasting” for up to 72 hours.

No STIMULATING MEDS for 3 days to 3 weeks (see list).

No exercise the day or night before.

Drawn in AM.
Is this IGF-1 worth it?

Yes.

Can tell you a lot about your patient.

Can allow you to properly make the diagnosis of AGHD (Adult Growth Hormone Deficiency).

Or diagnose a HGH-eluting pituitary tumor.

Or malnutrition such as vitamin deficiencies.
What is STIM testing?

A physician’s attempt to stimulate the pituitary to elute HGH.

Usually an ITT or Arginine Stim test.

ITT is brutal.

Arginine does not work very well.
INSULIN CHALLENGE TESTING

(Is 99% of the time an insurance construct/hurdle/requirement and NOT a diagnostic requirement.)
What is ITT?

Insulin Tolerance Test.

Insurance companies prefer this.

No reimbursement to doctor for doing this 5 hour dangerous test.

Fasting patient – give 10u regular insulin IV to drop BS <40 for 4hrs.

Then draws HGH levels every 1/2 hour.

ITT is brutal & dangerous (seizure or MI or both).

Few endocrinologists know how to perform.
How and why does one need stimulation testing?

Insurance, in order to reimburse for HGH, throws it up as an impossible hurdle but demands it any way.

HGH will rarely be reimbursed despite positive ITT.

Constant fight.

You can never make them happy.
SO INSTEAD, WE GET AN IGF-1!
What is an IGF-1?

The subhormone of HGH that hangs around the longest after the breaking apart of the super large HGH

IGF-1 benefits many but downsides too.
IGFBP-3 naturally offsets downsides.
What is considered to be a HIGH IGF-1?

IGF-1 varies according to age.

Teenagers can and should have very HIGH IGF-1 so do not be shocked – the taller the teenager the higher the IGF-1.

A properly obtained IGF-1 above 300 ng/mL is usually high for an older adult.

Above 650 ng/mL for a teenager.

Must have symptoms of high HGH (early acromegaly symptoms) – muscle and joint aches are the earliest.
Symptoms of too much HGH for too long...

- Rings won’t fit (too small).
- Shoes won’t fit (too small).
- Overall muscle and bone aches.
- Frontal brow bossing (bad).
- Frontal jaw enlargement (bad).
Can you diagnose a growth hormone producing tumor off of a high IGF-1?

If properly obtained it should make you worry.

Remember to ask what meds they were on etc.

Repeat under “perfect” circumstances to confirm.

Get prolactin level next too.

Any recent history of trauma?

Get 3T MRI with contrast! (Why?)

Then neurosurgery consult.
A nice IGF-1 range card

Table 2. Mean, median, lower (2.5th percentile, mean - 2 SD) and upper (97.5th percentile and mean + 2 SD) limit of IGF-1 (μg/L) according to age group

<table>
<thead>
<tr>
<th>Age group</th>
<th>2.5th percentile</th>
<th>Mean - 2 SD*</th>
<th>Mean</th>
<th>Median</th>
<th>97.5th percentile</th>
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<td>66-70 years</td>
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<td>65</td>
<td>110</td>
<td>110</td>
<td>185</td>
<td>188</td>
</tr>
</tbody>
</table>

* Of log-transformed values converted to the corresponding original value.
High IGF-1 in an 18 year old male.

Why is it so high?

Why is his testosterone so low?

Was this properly obtained?

Does his age matter?

He was not fasting – is that important?

Maybe he was on an anti-depressant – does that matter?
What is a **LOW IGF-1**?

This depends on age primarily.

Young teenagers, or young adults should be very high usually. –300-600+ng/mL

If below 100ng/mL, properly drawn, and they have symptoms then strongly positive for AGHD.

(Remember get a PROLACTIN level to make sure no prolactinoma. Prolactin can be exuded after trauma too.)
Can you diagnose a **Adult Growth Hormone Deficiency** based on a **low IGF-1**?

If properly obtained.

And has symptoms of **AGHD**.
Symptoms of AGHD

- Fatigue
- Brain fog
- Moderate to BEYOND SEVERE Insomnia
- PTSD
- Feelings of impending doom or death
- Feelings of hopelessness
- These are usually bad symptoms
- Short stature (< 5’0”)
*POSSIBLE TEST QUESTIONS TODAY*
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Under what circumstances should you strive to get a proper IGF-1?

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Drugs that affect IGF-1 levels?

Does exercise affect IGF-1 levels?

Does diet affect IGF-1 levels?

Does sexual activity affect IGF-1 levels?

Do other hormones affect IGF-1 levels?

Does IGF-1 level affect other hormone levels?
Under what circumstances should you strive to get a proper IGF-1?

Someone with severe insomnia and fatigue.

S/P a significant TBI.

S/P a LOC event.

Someone who cannot heal properly.

Someone who hurts all over (similar to fibromyalgia).
Does HGH (i.e. IGF-1 levels) affect other hormone levels? Or vice versa?

Low IGF-1 could give a falsely low value to testosterone levels (male or female).

A low testosterone level will do the same to IGF-1.

They tend to act copasetically or in tandem (usually but not always).
Can trauma affect IGF-1 levels?

YES but of course it varies.

Big surge directly afterwards from a freshly or recently damaged pituitary (TBI or LOC event) [SO DON’T BE FOOLED].

After weeks or months the level could drop to below 100 ng/mL or lower (11?).

Gets lower or worse over time.

Can take a year or two or three (YES 3!!!) in younger people so watch them closely.
Can TBI affect IGF-1 levels?

Yes, but not always.

Get an IGF-1 as soon as the trauma has occurred.

Follow longitudinally for at least 6 months to 3 years.

LOC event guarantees at least some anterior pituitary dysfunction.
TBI causing pituitary dysfunction in a younger athlete – takes a while.

Their levels are so high it can take years.

Warn the parents and coaches.

Watch over them.

Get a “baseline” IGF-1 as soon after the trauma as you can.

If possible, keep using the same lab.
PATIENT EXAMPLES
PATIENT #1
A young guy with low tes and high HGH – WHY?
A young guy with low testes and high HGH – WHY?

Summary of Deficient Test Results

Testing determined the following functional deficiencies:

- **Vitamin B12**
- Borderline deficiencies include:
  - Pantothenate
  - Choline
  - Chromium
  - Zinc
  - Copper

MTHFR Genotype Test Result

**Test**
- C677T Mutation
- A1298C Mutation

**Result**
- Heterozygous
- Negative

This sample has two copies of the C677T mutation and is negative for the A1298C mutation. This genotype:
- is associated with decreased enzyme activity (approximately 30% of normal activity).
- is associated with increased homocysteine levels.
- is correlated with increased risk of cardiovascular disease or thrombosis.
- is associated with potential methotrexate intolerance and patients may require dosage adjustments or discontinuation.

John F. Crawford, Ph.D.
Laboratory Director

MTHFR Background Information

MTHFR (methyltetrahydrofolate reductase) is an enzyme involved in the metabolism of folate and homocysteine. It plays a role in maintaining cellular folate levels and is a cofactor needed to convert homocysteine (a potentially toxic amino acid) to methionine.

Certain common genetic point mutations have been characterized that reduce the function of the MTHFR enzyme. These are the C677T mutation (which is a change from cytosine to thymine at position 677 within the gene) and the A1298C mutation (which is a change from adenine to cytosine at position 1298 within the gene). An MTHFR enzyme with reduced function can lead to elevated homocysteine levels, which is a known independent risk factor for development of cardiovascular disease and venous thrombosis. Reduced enzyme function can also affect folate status.

An additional area in which the function of MTHFR can have an effect is during methotrexate therapy. Methotrexate is a drug often used in treatment of certain cancers or autoimmune diseases. It is a structural analogue of folate and can interfere with folate metabolism. Defects in folate metabolism such as those potentially arising from mutations affecting MTHFR function can increase sensitivity to methotrexate and may lead to lower dosage requirements, increased side effects, or intolerance of the drug.

Testing Limitations

Only the C677T and A1298C mutations are analyzed in this assay. There may be other unknown non-genetic factors or genetic factors besides the tested mutations that can affect homocysteine levels, folate status, or drug sensitivities. Rare mutations in the primer binding sites used to detect the C677T and A1298C mutations may prevent detection. Specific dosing guidelines for methotrexate based on MTHFR genotype are not currently available.

MTHFR genotyping can provide useful information concerning risks of developing cardiovascular disease or thrombosis, or potential for increased sensitivity to methotrexate treatment. However, genotyping alone is not predictive of development of disease or complication and should not be used as the primary means of clinical diagnosis or treatment decision making. This information should be used by a physician in conjunction with additional clinical information to determine an appropriate treatment regimen.
He was 18 and almost always their HGH is at peak output at that age.

He was not fasting.

He had exercised that morning in PE.

He was on Effexor (which we stopped).
Patient #2
Remember **Not all AGHD is from PITUITARY TRAUMA...**

Total Tes 459
FT3 2.5

---

### Intermountain Healthcare
**Lab Results**

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<td>FT3</td>
<td></td>
<td>2.5 ng/dl</td>
<td>Serum or Plasma</td>
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Interpretation of PSA:
There is no cutoff for PSA with simultaneous high Total Testosterone.
Remember Not all AGHD is from PITUITARY TRAUMA...
Remember Not all AGHD is from PITUITARY TRAUMA...

Account Number:
Danny Purser, M.D.
383 W. 600 North
Lindon, UT 84042
USA

Name:
Gender: Male
DOB: 05/13/1967

Accession Number:
Requisition Number:

Date of Collection: 04/18/2016
Date Received: 04/19/2016
Date Reported: 04/28/2016

Summary of Deficient Test Results

Testing determined the following functional deficiencies:

- Oleic Acid
- Coenzyme Q-10
- Vitamin D3
- Vitamin C
- Vitamin A
- Copper
- Zinc

Borderline deficiencies include:

- Manganese
- Spectrox
- Insulin
- Immunidex
- Magnesium
- Glutathione

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**Spectrox**

![Graph showing Spectrox levels]

**Immunidex**

![Graph showing Immunidex levels vs Age]
Ahah! He had **Hetero C677T**

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<th>Gene &amp; Variation</th>
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*Lithium Orate 5 mg to 5 mg 2/3*  
*Be (Riboflavin) 25 mg to 100 mg*  
*Natural Phytomenadione*  
*Rauwolfia Serpentina 10 mg O/D*  
*Avoid Methyl Donors*
PATIENT #3
Interesting Labs on a 59 yo lady

Opinions on Free Tes levels in women?

| Testosterone, Free, Direct | 1.7 | pg/mL | 0.0 - 4.2 | 02 |

Thyroid Antibodies

| Thyroid Peroxidase (TPO) Ab | 11 | IU/mL | 0 - 34 | 01 |
| Thyroglobulin Antibody | Will Follow | IU/mL | 0.0 - 0.9 | 01 |

Vitamin B12

| 518 | pg/mL | 232 - 1245 | 01 |

Progesterone

| 1.9 | ng/mL | Follicular phase | 0.1 - 0.9 |
| Luteal phase | 1.8 - 23.9 |
| Ovulation phase | 0.1 - 12.0 |

Pregnant

| First trimester | 11.0 - 44.3 |
| Second trimester | 25.4 - 83.3 |
| Third trimester | 58.7 - 214.0 |
| Postmenopausal | 0.0 - 0.1 |

Insulin

| 4.8 | uIU/mL | 2.6 - 24.9 | 01 |

Ferritin, Serum

| 55 | ng/mL | 15 - 150 | 01 |

**Triiodothyronine (T3), Free**

| 6.5 | High | pg/mL | 2.0 - 4.4 | 01 |

**M005-IgG Candida albican**

| 26.9 | High | ug/mL | 0.0 - 1.9 | 02 |

**

This test was developed and its performance characteristics determined by LabCorp. It has not been cleared or approved by the Food and Drug...
Interesting Labs on a 59 yo lady

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
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<td>ng/mL</td>
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Your thoughts on this IGF-1 lab result and range?
Can aging cause pituitary decline?

No, but trauma can.

“Aging” is not just a magical blanket disease but life itself is associated with specific incidents, diseases, and traumas that can cause a decline.

Malnutrition/Malnourishment can.

 Genetic malnutrition can (i.e. MTHFR, MTRR, etc)

And just being weird does not cause pituitary damage either.
Is HGH safe to give?

**Prospective safety surveillance of GH-deficient adults: comparison of GH-treated vs untreated patients.**


**Collaborators (173)**

**Author information**

\(^1\)Lilly Research Laboratories, Indianapolis, Indiana 46285, USA.

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**CONCLUSIONS:** In GH-deficient adults, there was no evidence for a GH treatment effect on death, cancer, intracranial tumor recurrence, diabetes, or cardiovascular events, although the follow-up period was of insufficient duration to be conclusive for these long-term events. The identification of unexpected GH-related AEs reinforces the fact that patient selection and GH dose titration are important to ensure safety of adult GH replacement.
REFERENCES


