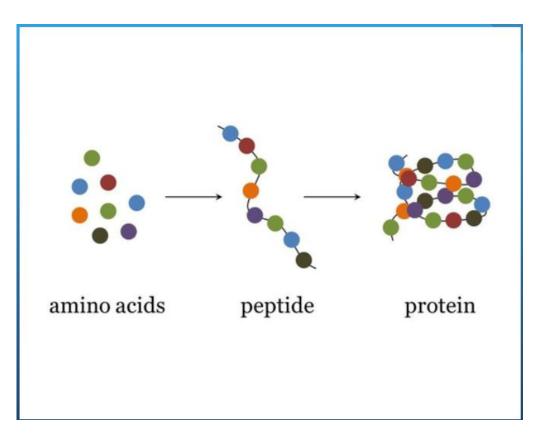
William Clearfield D.O. COME 2.0, Spring 2020 Executive Director American Osteopathic Society of Rheumatic Diseases

Introduction to Peptides

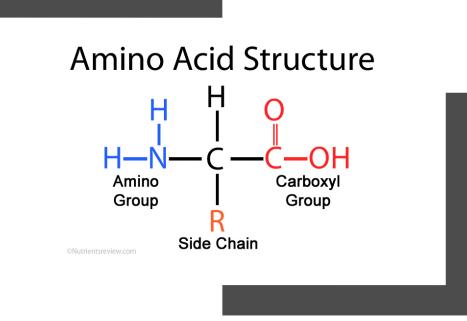
C-1-)+Q

1)00

Amino Acids, Proteins and Peptides, Oh My!



Amino Acids, Proteins and Peptides, Oh My!



- Groups of organic molecules composed of:
 - Amino group $(-NH_2)$
 - Acidic carboxyl group (—COOH),
 - Organic side chain (R group).



Amino Acids, Proteins and Peptides

- Essential Amino Acids:
 - Exogenous to the body
 - Taken in the form of food or other means.
 (Intravenous, transdermal or liquid).
 - Nine Essential A.A.
 - Histidine, Isoleucine, leucine, lysine, methionine, phenylalanine, threonine, tryptophan, and valine

Amino Acids, Proteins and Peptides

• Non-essential amino acids:

– Internally generated

 alanine, arginine, asparagine, aspartic acid, cysteine, glutamic acid, glutamine, glycine, proline, serine, and tyrosine

Amino Acids, Proteins and Peptides

- Conditional A.A.
 - Non-essential except in time of stress
 - arginine, cysteine, glutamine, tyrosine, glyci ne, ornithine, proline, and serine

Amino Acids, Proteins and Peptides, Oh My!

ğ

*T*wo or more amino acids linked by a peptide bond in a chain



Protein chains are > 50 A.A. Combinations



Enables



Amino Acids, Protei ns and Peptides



Structurally similar to proteins



Contain less than 50 amino acid chains.



"Oligopeptides," substances with less than twenty, or *"polypeptides,"* consisting of 21-50 amino acids



Sequence, shape, and type of amino acids involved determine a peptides' function.

Introduction to Peptides





7000 KNOWN PEPTIDE SEQUENCES 500 WITH SORT OF THERAPEUTIC VALUE



60 APPROVED (FDA) AS MEDICATIONS.



- "A-G-E ing" = 4-letter word
- Built-in senescence=
 - Collagen breaks down.
 - Skin thins and wrinkles =
 - Damaged collagen layer
 - Message "We need more collagen."
 - Peptides produced, "messengers"
 - Regenerated tissues are incompletely repaired
 - Vicious cycle of breakdown and "disability" of the integumentary system.



- XYZ Collagen Skin Repair Cream
 - Peptides
 - The skin "misremembers" its' repair sequence
 - Accelerates the rate of new collagen restoration.

Peptides Vs. Hormones



1st Peptide isolated: Insulin



Peptides are Tissue Specific



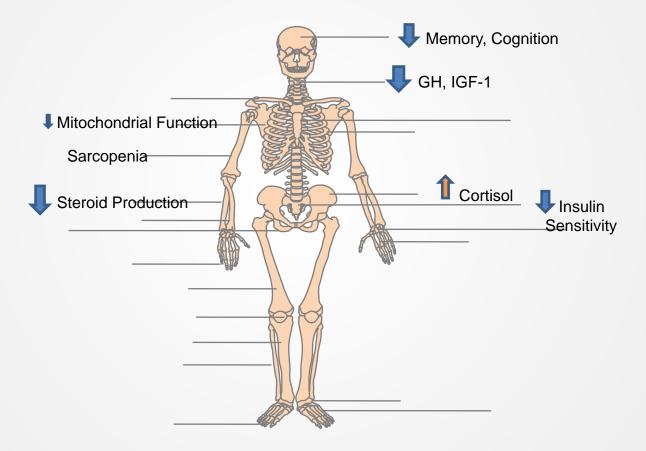
Hormones act globally on body



Mitochondrial Messenger

Intimately involved in the inflammatory process







Peptides

- Immune enhancement
- Sleep
- Memory
- Depression/anxiety
- Improved cognition esp. post TBI
- Antimicrobial, anti-viral, anti-fungal, and antiparasitic agent
- Cellular rejuvenation and restoration
- Pain relief.

Peptides Act As A Fine Tuning Mechanism

Hormones

- Immune system
- Sleep
- Inflammatory cytokines
- Cell renewal
- Cancer cell destruction
- Libido

- Sexual arousal
- Weight loss
- ✤ Lean muscle gain
- Wound healing
- Brain function
- Urinary System
- Reproductive System.

Favorite Peptides

- Growth Hormone Mimetics
 - GHRH
 - Semorelean
 - CJC 1295 +/- DAC
 - GHRP
 - GHRP 2
 - GHRP 6
 - Ipamorelin
 - Hexarelin
- Immune Modulating Peptides
 - Thymosin Alpha 1 (TA1) (increases TH1)
 - Thymosin Beta 4 (Tβ4) (increases TH1/decreases TH2))
 - BPC-157 (decreases TH2/healing hormone) (oral, SQ, nasal, eye drops) "Homeostasis Peptide."
 - Synergistic with pineal protein Epithalon
- Rejuvenation/Pain
 - BPC-157, TB4, Epithalon, DSIP, GHRH/GHRP

Favorite Peptides

- Brain peptides (memory, depression, anxiety, TBI, brain function, etc.)
 - Cerebrolysin
 - Semax
 - Selank
 - Synergistic with Epithalon, TB4, BPC-157, DSIP

Sleep peptides

- Epithalon "Homeostasis Peptide"
- Delta sleep-inducing peptide (DSIP)
- CJC/Ipamorelin (GHRH/GHRP) (other combo's)
- AOD

Antimicrobial peptides

- LL-37 (effective against Lyme cysts, viruses, fungal, parasites) (synergistic with TA1)

Peptide Summary

	Class	Pain	Immunity	Inflammation	Libido	Anti- Aging	Weight Loss	Cognitive	Antioxidant	Sleep	Dose	Conditions
PT-141	MSH Analog				+++		+				1-2 mg 2x/d	Libido, Weight Loss, Tanning
GHRH/GHRP	HGH Mimic		+	+		+	+	+		++	160-400mg @ hs	Healing, Body Fat, Rejuvenation
Semax	Nootropic	+	+	++	+	+++		+++	++	+	100-300 mg/d	Cognitive Dysfunction, Memory,
Selank	Nootropic		+	+		+		++	+	++	100-300 mg/d	Dementia, Stroke, TBI
CJC/Ipamorelin	GHRP/GHRH		+	+		++	+	+		++	150-300 mg/d	GH Stimulation

Peptide Summary

	Class	Pain	Immunity	Inflammation	Libido	Anti- Aging	Weight Loss	Cognitive	Antioxidant	Sleep	Dose	Conditions
Thymosin Alpha 1	TH 1 Stimulation	+	+++	++		++		+	++		50-300 mcg/d	Immune boost; CA, Infections
Thymosin Beta 4	TH1/TH2 Balance	++	+++	+++		++		++	++	+	50-300 mcg/d	Immune modulation, CA, Neurorejuvenation, muscle pain
BPC 157	Anti inflammatory	+++	+++	+++		+++	+	+	+++	+	Oral 500 mg 1- 4/d/50-200 2/d	Wound healing, orthopedic repair, GI Healing, rejuvenation
Epithalon	Pineal Peptide Gland	÷	++	++		+++		++	+++	+++	50-150mg/d	Anti-biofilm, infections, Lyme, anti- bacterial, antibiotic, antiviral, antiparasitic

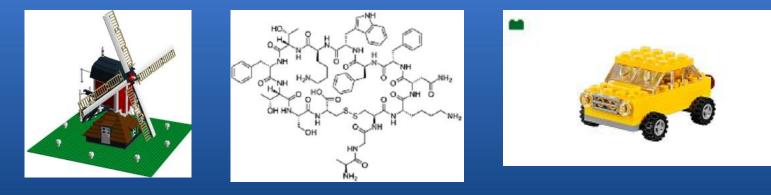


Growth Hormone

William Clearfield D.O. Nevada Homeopathic and Integrative Medicine Association September, 2019

Growth Hormone

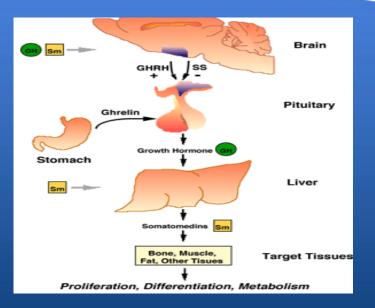
 A "Lego-like" 191 amino acid polymer linked in a specific manner in a specific order.



 Growth Hormone stimulates growth and cell reproduction

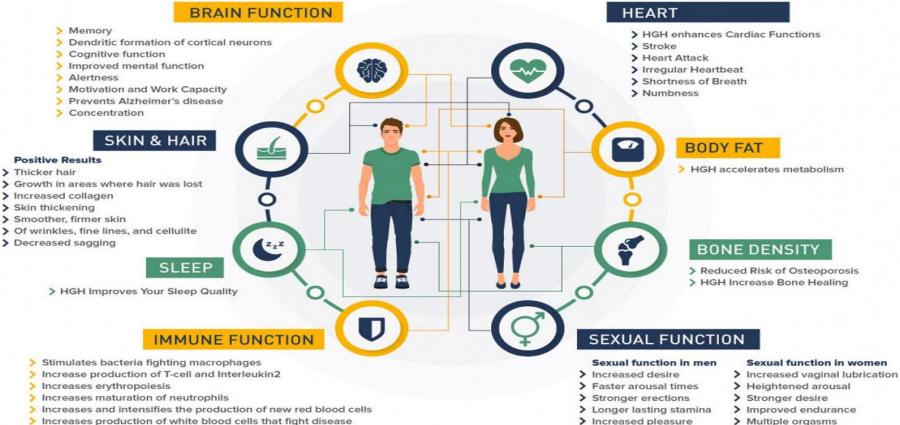
http://marshanunleymd.files.wordpress.com/2011/05/hgh-dna-sequence1.gif

Growth Hormone Production



- Secreted in Anterior Pituitary
- Peak Production Between 10 PM and 4 AM

HUMAN GROWTH HORMONE BENEFITS



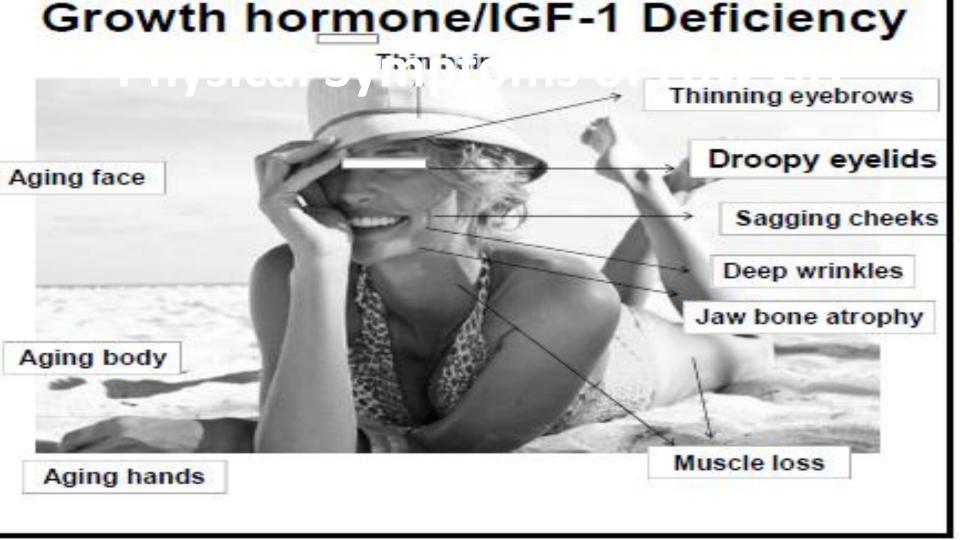
Increases production of white blood cells that fight disease

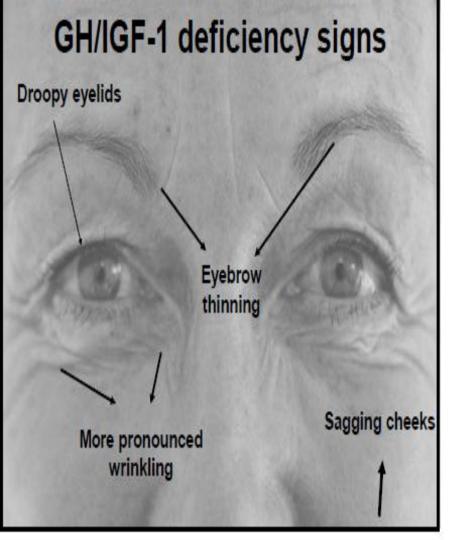
> Multiple orgasms

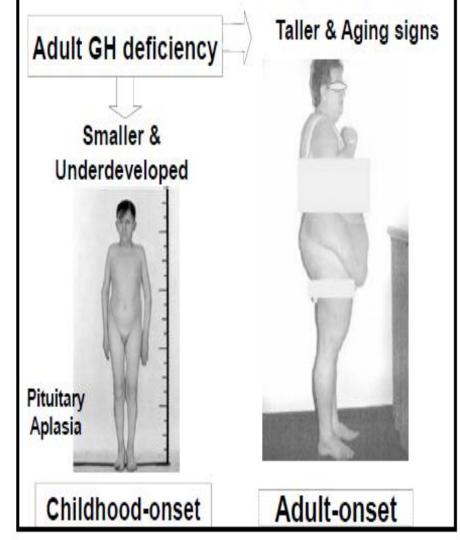
Growth Hormone Deficiency

- Anxiety/Depression
- Paranoia
- Memory/Concentration Loss
- Fatigue
- Insulin Resistance
- Temperature Sensitivity
- Weight Gain
- Increased LDL

- Sarcopenia
- Dry Skin
- Reduced Bone Density
- Reduced Muscle Tone
- Increased LDL
- Decreased Confidence
- Diminished Immune Function
- Increased Triglycerides







Rudman, 1991

• 8.8 percent increase in lean body mass

• 14.4 percent decrease in adipose-tissue mass

• 1.6 percent increase in average lumbar vertebral bone density (P less than 0.05 in each instance).

• Skin thickness increased 7.1 percent.

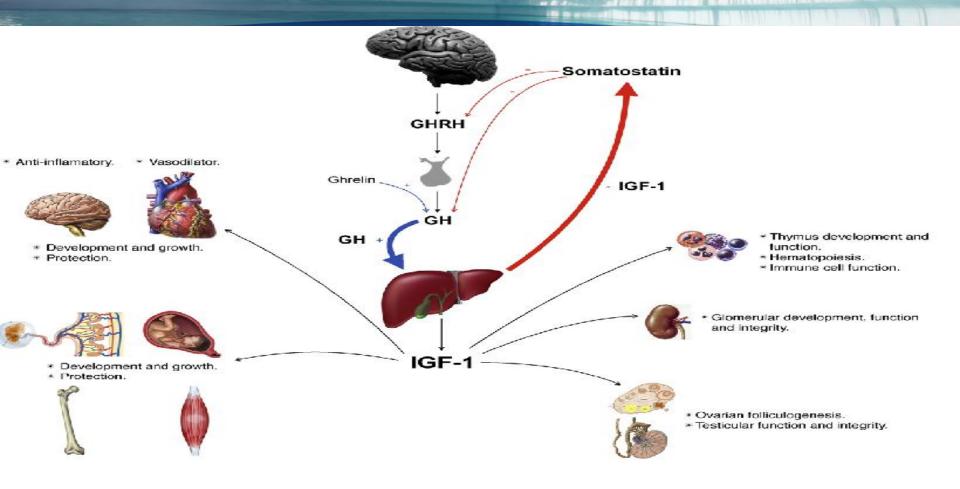
RX: 0.03 mg of Biosynthetic HGH per kilogram of body weight SQ 3x/week

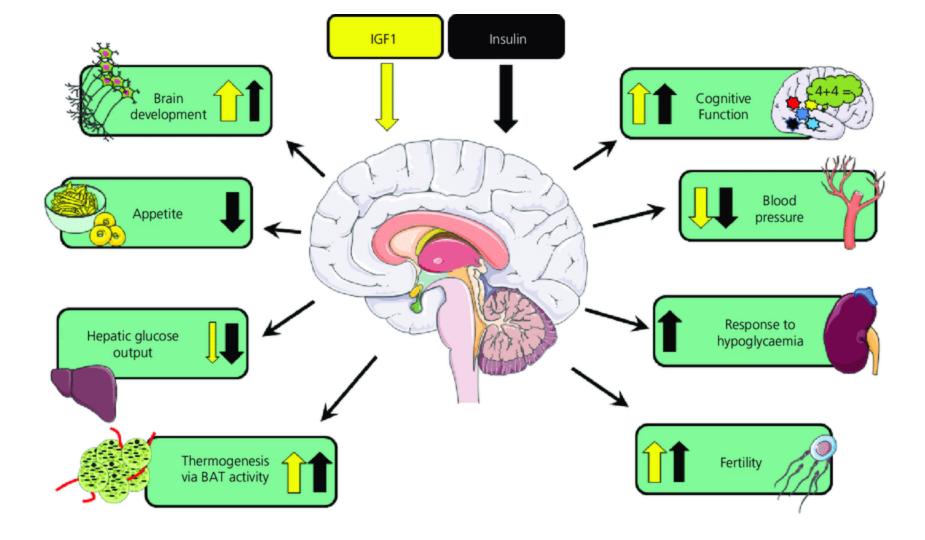
Rudman D, Feller AG, Cohn L, Shetty KR, Rudman IW, Draper MW. Effects of human growth hormone on body composition in elderly men. Harm Res 1991;36 Suppl 1:73-81

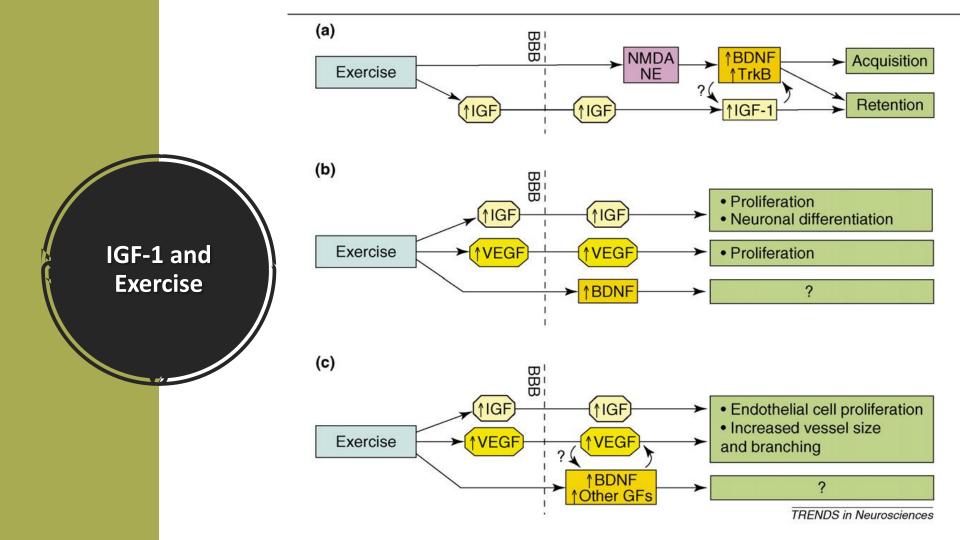
IGF-I

Downstream Active Ingredient of Growth Hormone

Downstream Active Ingredient of Growth Hormone







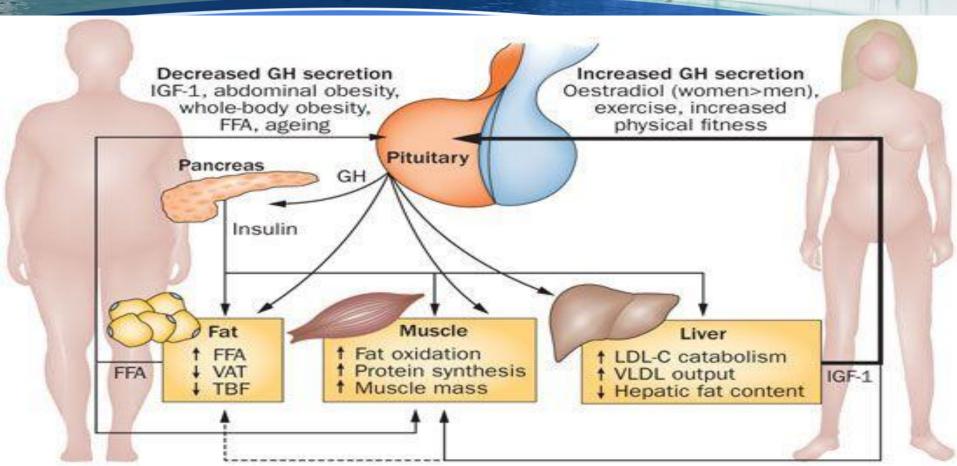
IGF-1 and Immunity

• JGF1 signaling = Immunocompetence



B cell responses Natural killer activity Macrophage activity T-cell function Immune Cell Production

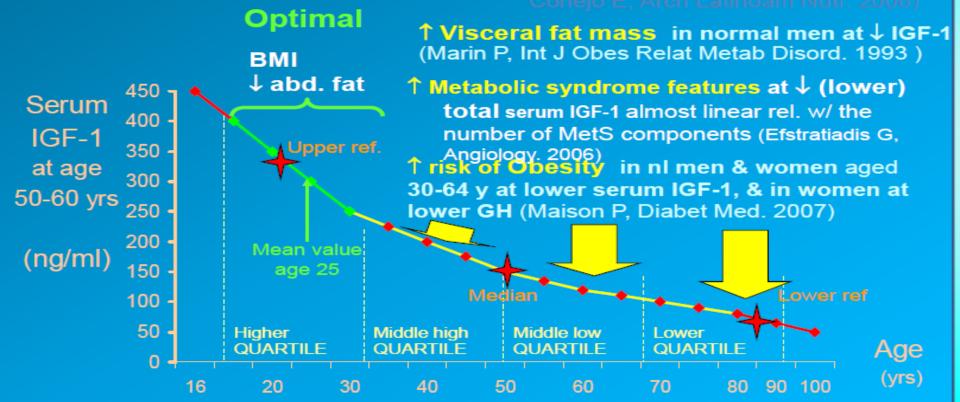
GH/IGF-1 in Obesity



Sign. Inverse Assoc. of serum IGF-1 & Obesity

Body mass index in normal boys at various stages of puberty & young adulthood (7-27 yrs) at lower 24-h serum GH & serum IGF-1 (Martha PM, J Clin Endocrinol Metab. 1992)

↑ Body mass index & obesity index in adolescent boys & girls (13-18 y) at lower serum GH (Molero-

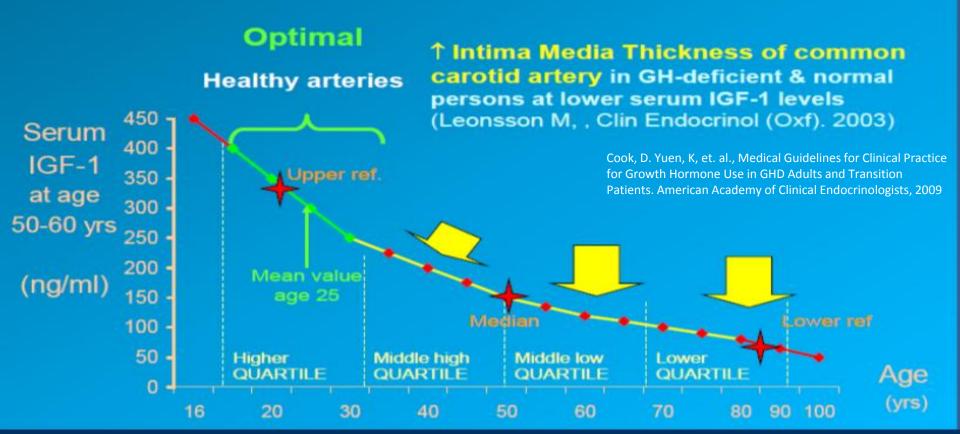


Growth Hormone and Cardiovascular Risk

- Abnormal body composition
- Unfavorable lipid profile
- Increased fibrinogen
- Increased C-reactive protein levels
- Insulin resistance
- Early atherosclerosis
- Endothelial dysfunction
- Impaired left ventricular (LV) performance

[•] Colao A et al. Beginning to end: Cardiovascular implications of growth hormone (GH) deficiency and GH therapy. Growth *Horm IGF Res.* 2006 May 9 **13**

Sign. Inverse Ass. of serum IGF-1 & Atherosclerosis GHD Patients = 9-fold incidence of cardiovascular mortality



Sign. inverse Assoc. of serum IGF-1 & Cancer stage

OPTIMAL

 Less severe cancer

450 -

400 -

350

300

Serum

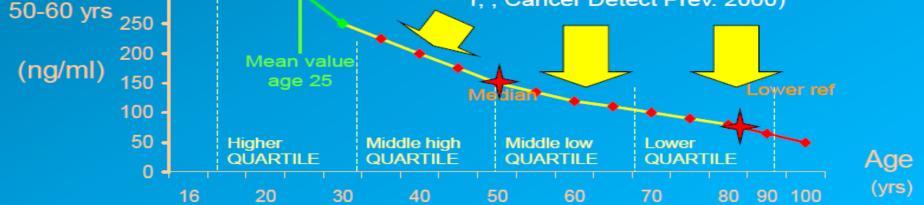
IGF-1

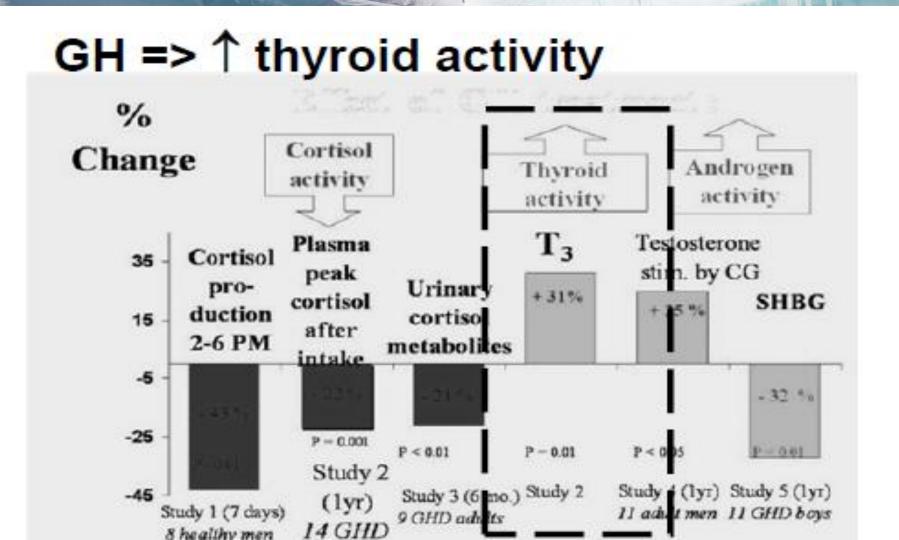
at age

No metastasis

Upper ref.

↑ TNM (tumor-node-metastasis) stage At ↓ (lower) serum IGF-1 in breast cancer patients, despite a higher serum IGF-1 in BC patients vs controls, & after adjustment, te serum IGF-1 remained sign. & positively assoc. with breast cancer risk (odds ratio, 1.183; 95% CI: 1.167-1.201). (Agurs-Collins T, , Cancer Detect Prev. 2000)





Schizophrenia => ↓ Growth Hormone



Tensed body at night: ↓ melatonin

Positive symptoms of schizophrenia

= psychotic behaviors not seen in healthy people

- Delusions: false beliefs that are not part of the person's culture and do not change. The person believes delusions even after other people prove that the beliefs are not true or logical.
- Thought disorders are unusual or dysfunctional ways of thinking, for example: "disorganized thinking"
 a person has trouble organizing his or her thoughts or connecting them logically.
- Hallucinations: things a person sees, hears, smells, or feels that no one else can see, hear, smell, or feel. "Voices" are the most common.

Reduced or cured by growth hormone therapy: => GH improves logical and sound thinking, evidence-based beliefs, accurate senses

58

Kahn RS, Davidson M, Hirschowitz J, Stern RG, Davis BM, Gabriel S, Moore C, Davis KL. loctumal growth hormone secretion in schizophrenic patients and healthy subjects. Psychiatry Res. 1992 Feb;41(2):155-61. 57

First and most common deficiency

- Acute Injury Incidence rate: 20%.
- 12 month follow up rate increases to 35-40% of survivors.

- 1. Aimaretti, G; et al., Hypopituitarism and Growth Hormone Deficiency after TBI. Growth Hormone IGF Res 2004 June 14 Suppl A:S114-7
- 2. Agha A. Phillips J. Thompson C.J. Hypopituitarism following traumatic brain injury (TBI) Br. J. Neurosurg. 2007;21:210–216.
- 3. Kelly DF, McArthur DL, Levin H, et al. Neurobehavioral and quality of life changes associated with growth hormone insufficiency after complicated mild, moderate, or severe traumatic brain injury. *J Neurotrauma*. 2006 Jun;23(6):928-42.
- 4. Leon-Carrion J, Leal-Cerro A, Cabezas FM, et al. Cognitive deterioration due to GH deficiency in patients with traumatic brain injury: a preliminary report. *Brain Inj.* 2007 Jul;21(8):871-5.

Memory

Concentration

Mental clarity

OCD

Dark moods

Paranoia

Poor Concentration

Anxiety

Rapid weight gain

Excessive anxiety

Depression along

Poor overall physical health and quality of life

Deficits in:

Attention

Executive Functioning

Cognitive & Mental Abilities to Achieve Goals Memory

Emotion

Mood Anxiety/Depression

- Correction of GHD :
- Tempers:
- Intensity of Outbursts
- Hostility
- Paranoid Ideation
- Anxiety, Phobia
- Somatization
- Obsessive Compulsive S/S

• Improves:

- Verbal and Non-Verbal Memory
- Cognition
- Mental Alertness
- Work Capacity

[•] Cook, D. Yuen, K, et. al., Medical Guidelines for Clinical Practice for Growth Hormone Use in GHD Adults and Transition Patients. American Academy of Clinical Endocrinologists, 2009

Growth Hormone in the Immediate TBI Time Frame

 Balancing GH, Thyroid Hormone and LH/FSH Axis Hormones in the immediate post trauma (within 48 hours) time frame decreased mortality by 50%.

Mortality rates evened out with placebo within 30 days.

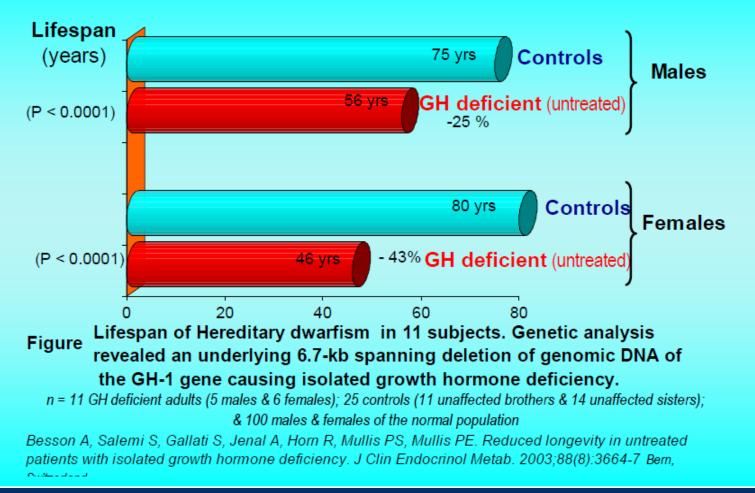
Wright, D.W., Randomized Clinical Trial of Progesterone for Acute Brain Injury,; Annals of Emergency Medicine; 2006 07; 932

L-Dopa Raises Growth Hormone

- Oral doses (0.5 g) caused a significant rise in plasma GH.
- The rise in plasma GH persisted for 120 minutes after the administration of the drug.
- The data suggest that a dopaminergic mechanism in the median eminence or a norepinephrine-sensitive site in the hypothalamus or limbic system may be involved in the regulation of growth-hormone secretion.
- Parkinson's disease patients, on L-dopa therapy, enjoy an elevated plasma GH for a substantial part of the day

Stimulation of Human-Growth-Hormone Secretion by L-Dopa. N Engl J Med 1970; 283:1425-1429 Dec. 24. 1970. A. E. Boyd, III, M.D., Harold E. Lebovitz. M.D., and John B. Pfeiffer, M.D. From the divisions of Endocrinology and Neurology, Department of Medicine, Duke University Medical Center

Untreated GH deficiency => 11 mortality



GH therapy => prolongs life (\$\frac{1}{2}\$ the increased mortality of) in GH deficient patients

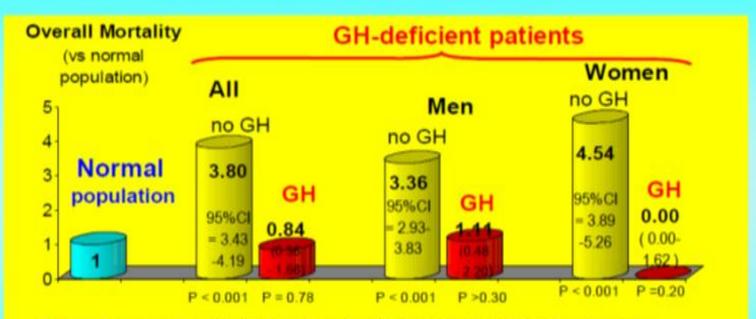


Figure: Overall mortality & the rate of myocardial infarctions were increased in hypopituitary patients without GH replacement, GH replacement normalized the risk.

J. Svensson, B.-A. Bengtsson, T. Rosén, A. Odén, G. Johannsson. Malignant Disease and Cardiovascular Morbidity in Hypopituitary Adults with or without Growth Hormone Replacement Therapy . J Clin Endocrinol Metab. 2004 Jul;89(7):3306-12

Side Effects of GH

• Think PAGE:

1.Paresthesia
2.Arthralgias
3.Glucose and insulin getting worse instead of better
4.Edema

GH Deficiency Diagnosis

Lab Values:
 GH 5.0 ng/ml
 IGF-1 200 ng/ml
 IGFBP-3 4000 ng/ml

Stimulation Tests

- Insulin Tolerance Test (Traditional)
- Glucagon Stimulation Test
- ✤ MRI R/O Pituitary Tumor
- Macimorelin (Approved 2017 by FDA)

GH Deficiency Macimorelin Challenge

 Dec 2017 FDA approved an orally available ghrelin agonist (GHRP)

- Macimorelin (Macrilen) is a non peptide, synthetic growth hormone secretagogue receptor agonist
- Macimorelin stimulates the secretion of growth hormone via the Ghrelin receptor
- 4 blood samples post oral administration of Macimorelin

• Garcia JW et al. The Journal of Clinical Endocrinology and Metabolism. 2013;98(6):2422-2429. doi:10.1210/jc.2013-1157

GH Deficiency Macimorelin Challenge

O.5 mg/kg PO single dose after 8 hr. fast

- Blood samples at 30, 45, 60, and 90 min.
- Test diagnostic if maximum GH level is:
 - <2.8 ng/mL for the 4 blood draws.</p>

Growth Hormone Treatment Algorithm

+Lab Evaluation

Secretagogue
 Retest 3 Mo.
 Increased → Continue 6 months then discontinue.
 Retest in 6 mo.
 No Change or Decrease → GHRH + GHRP
 Retest 6 mo.
 No Change or Decrease →
 5. Macimorelin or Insulin Stimulation Test



6. If + Consider HGH

Secretogogue #1

- Active Ingredients: Pyroglutamine, L-Glutamine, L-Arginine, L-Lycine, L-Valine, L-Tyrosine Alpha-ketoglutarate, L-Ornithine, Lalphaglycerlphosphoryl-choline, Gamma Amino Butyric Acid(GABA), and Mucina pruriens.
- Other Ingredients: Deionized water, Lecithin, Phospholipids, Sodium citrate, Citric acid, Maltodextrin, Potassium sorbate, Artificial color and Flavor.

Secretogogue #2

Arnica Montana 6X, Deer Antler Velvet 8X, Hepar Bovinum 6X, HGH 24X, 30X, IGF 1 8X, Pituitary Bovinum 5C, 7C, 9C, Thuja Occidentalis 6X

GH Deficiency Treatment

- Start low, go slow in titrating upwards
- Use HGH at bedtime
- Start at 0.1 mg SQ qhs
- Average dose is 0.3 mg to 0.5 mg SQ at bedtime
- Rarely 1 mg SQ at bedtime

• *IGF-1 typically increases 100 ng/dl with 0.33 mg/d Rx.*

Natural Enhancements of GH

Magnesium



Replete Mg Serum GH 8 %

Dørup I, Flyvbjerg A, Everts ME, Clausen T. Role of insulin-like growth factor-1 and growth hormone in growth inhibition induced by magnesium and zinc deficiencies. Br J Nutr. 1991 Nov;66(3):505-21.Institute of₄ Physiology, University of Aarhus, Denmark.

Natural Enhancements of GH

• Zinc

- A zinc deficiency equals an 83% drop in serum IGF
- Zinc repletion normalized serum zinc & increased serum IGF-1 by 194% (P < 0.05) after 3 days.
- Serum IGF-1 does not normalized until after 2.5 weeks of repletion.
- High zinc intake raises IGF-1 16%.
- Meat and fish modestly raise IGF-1 levels but never to height of zinc alone.

[•] Dørup I, Flyvbjerg A, Everts ME, Clausen T. Role of insulin-like growth factor-1 and growth hormone in growth inhibition induced by magnesium and zinc deficiencies. Br J Nutr. 1991 Nov;66(3):505-21.Institute of Physiology, University of Aarhus, Denmark

⁽²¹⁾ Larsson, Wolk, Brismar, Wolk, Association of Diet With Serum IGF-1 in Middle Aged and Elderly Men. Am. J. Clin. Nutr 2005 May 81(5)1163-7

GH Issues-Cancer

No increase in cancer

Children and adults treated with GH has revealed noincrease in observed cancer risk(Leukemia and Colon Cancer)

Endocrinology 2006, 64 (2): 115-121 P.J. Jenkins

25-year retrospective study -(1985- 2009)

Mortality rate from Cancer was not elevated in patients receiving GH

Van Bunderen CC, et al. <u>J Clin Endocrinol Metab.</u> 2011 Oct;96(10):3151-9

Long Term Safety of GH

- 28-year review of safety data from the manufacturers' GH Registries
- Data from 1988- 2016
- There was no increased risk of mortality in children or adults treated with GH
- There was no evidence of an increased risk of:
 - Stroke
 - New malignancy
 - Leukemia, non leukemic extra cranial tumors
 - No recurrence of intracranial malignancy in patients w/o risk factors (history of radiation Rx)

Legal Issues

- Reno HGH Trial: Jury Acquits Doctor
- Growth Hormone Deemed Illegal for Off-Label Antiaging Use
- Legal
 - Pediatrics
 - Growth hormone deficiency
 - Prader-Willi syndrome
 - Turner syndrome
 - Idiopathic short stature (when children are smaller than normal but there isn't a clear reason)
 - Growth failure in children born small who don't catch up by the time they are two.

Adults

- Growth hormone deficiency as a result of pituitary disease
- Radiation therapy
- Trauma.

Legal Issues

Illegal

 Bodybuilding
 Athletic performance
 Anti-aging

 Drug Enforcement Administration, Office of Diversion Control. "Human Growth Hormone" fact sheet; August 2013. http://www.deadliversion.usdoj.gov/drug_chem_info/hg .pdf

Peptides

• GHRH

- Sermorelin*
- ➢ CJC -1295
- > Tesamorelin*

• GHRP

- GHRP 2
 GHRP 6
 Ipamorelin*
 Hexarelin*
- GHRH + GHRP
 - CJC 1295 Ipmorelin

hGH vs Peptides Peptides offer the same benefits as h6H, without the risks.

	hGH (Somatropin)	hGH Peptides (eg. Sermorelin)
EFFECT ON hGH LEVELS	Promotes unnatural hGH levels Can shut down natural hGH production	Promotes natural release of hGH Promotes natural hGH production
EFFECT ON PITUITARY GLAND	Can negatively impact pituitary function	Supports pituitary function and health
SAFETY	hGH levels drop when therapy is stopped High risk of overdose Risk of Tachyphylaxis Associated with a range of side-effects including cancer	hGH production continues for a period even after therapy is stopped Very low risk of overdose No risk of Tachyphylaxis Minimal side-effects
ACCESSIBILITY	Controlled substance, hard to access legally	Readily available through legal means
соѕт	Higher cost (\$1,000+ per month)	Lower cost (\$200+ per month)
BENEFITS	All the benefits of healthy hGH levels	Same benefits as hGH, without the risks

GH Like Peptides

- Sub-groups of individual proteins
- Identified by their Growth Hormone-like properties
- Rearranged to accentuate the positive
- Limit the negatives





Better Living Through Chemistry-Anti-Aging and Sexual Enhancement Peptides

- Epithalon
 - A 4 Amino Acid Peptide Designed to Delay Mortality
- PT 141-Bremelanotide
 - Sexual Arousal Through Direct CNS Stimulation

The American Osteopathic Society of Rheumatic Diseases

OMED October 16-19, 2020 Austin, Texas

Congress of Medical Excellence 3.0 T.B.A.

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