GROWING PAINS:
WHAT WE KNOW ABOUT GROWTH HORMONE AND DOWN SYNDROME

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OBJECTIVES

- Review growth hormone physiology
- Review all published literature to answer 2 questions:

  1.Is the Growth Hormone Axis Dysregulated in Individuals with Down Syndrome?

  2.Is Growth Hormone Replacement/Supplementation EFFECTIVE and SAFE in patients with Down Syndrome?
- Discuss outstanding questions and ethical considerations

GH 101

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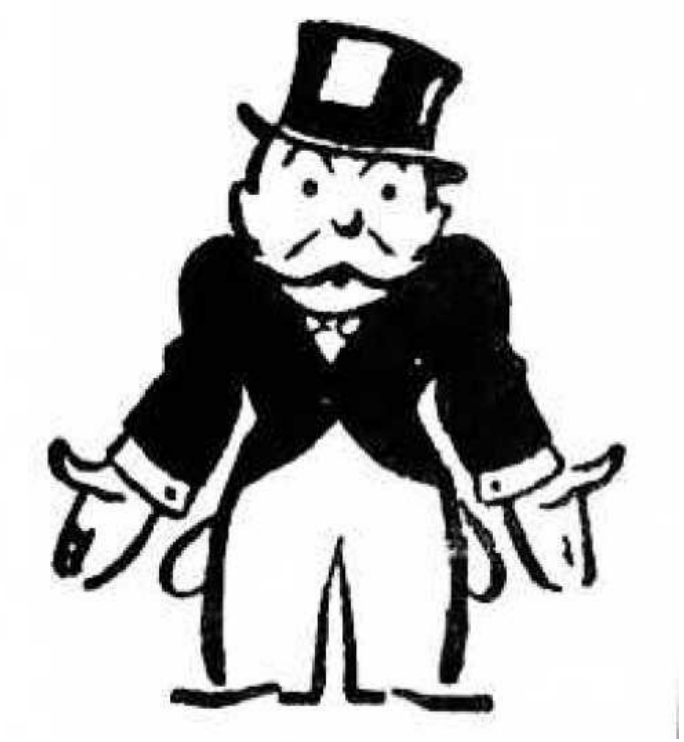
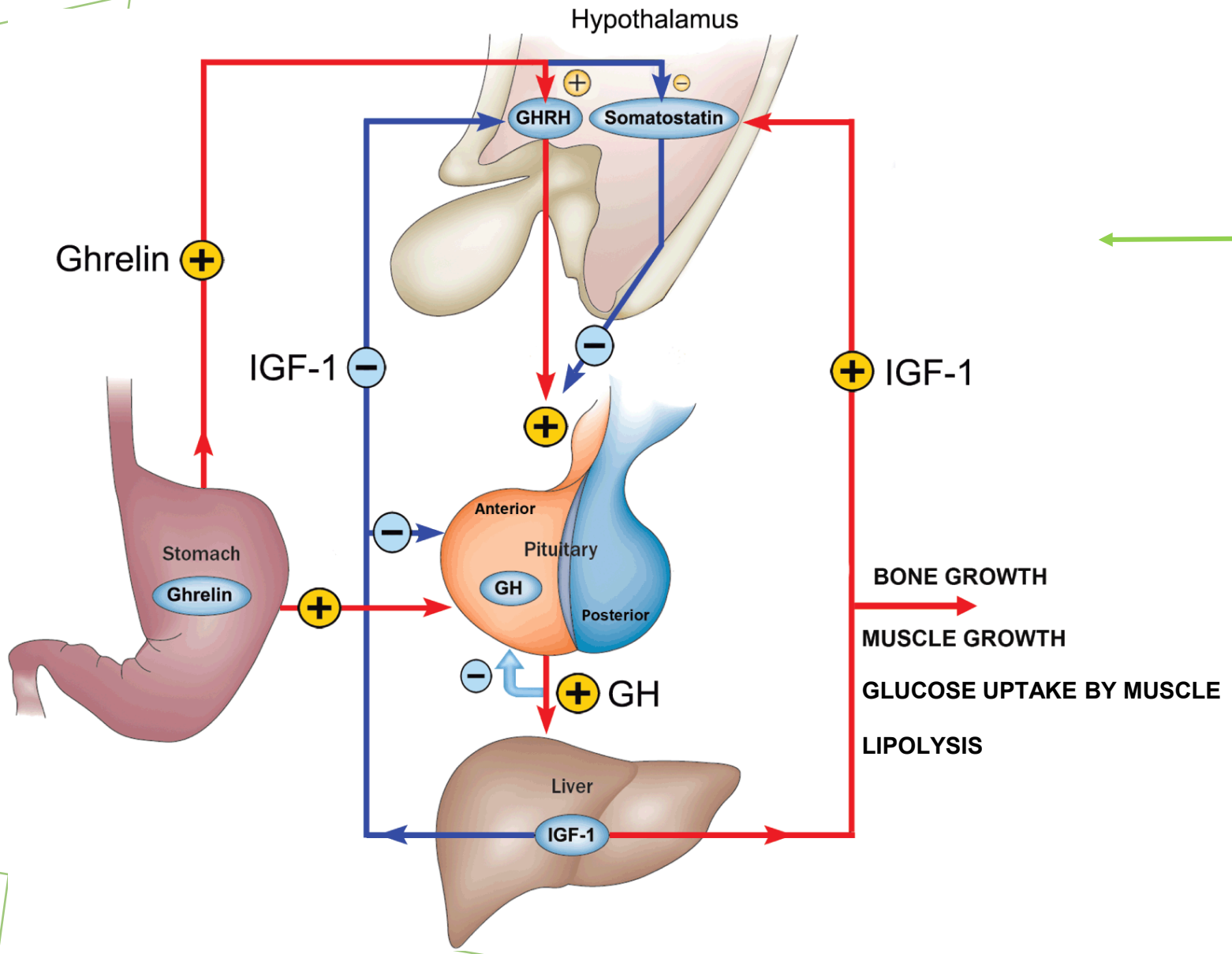
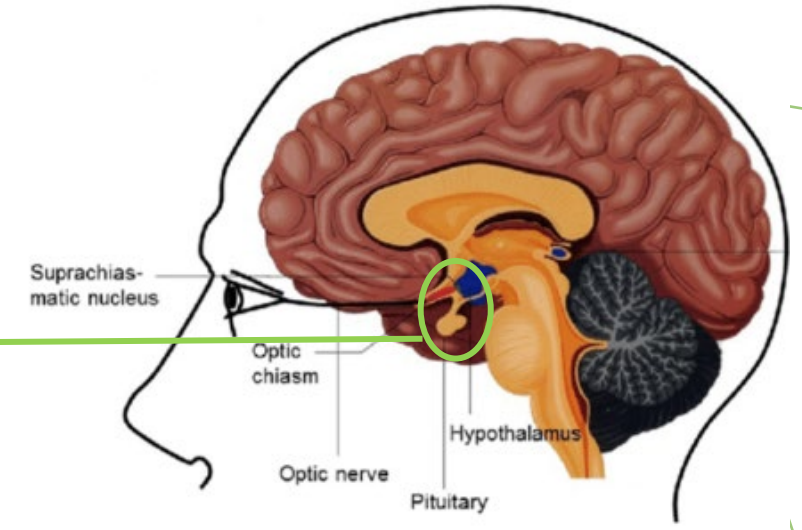
DISCLOSURES

- I am a consultant for Willow Laboratories, Inc.
- I have no financial relationships with any growth hormone companies
- I do intend to discuss unapproved/investigative uses of commercial products/devices in my presentation



WHAT IS GROWTH HORMONE?



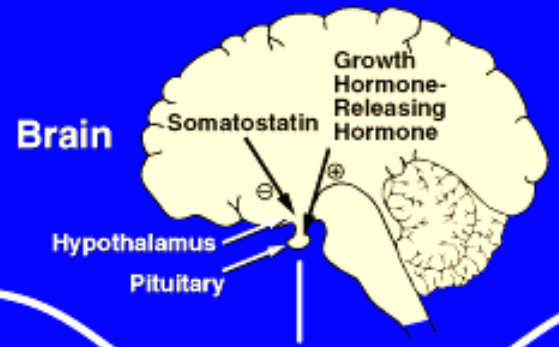


GHRH: Growth Hormone Releasing Hormone
Produced in the Hypothalamus

GH: Growth Hormone
Produced in the anterior pituitary

IGF1: Insulin Growth Factor 1
Produced in the liver and other peripheral tissues

Multiple Sites of Growth Hormone Action



Growth Hormone

Bone Metabolism

- Increase osteoclast differentiation and activity
- Increase osteoblast activity
- Increase in bone mass by endochondral bone formation

Muscle

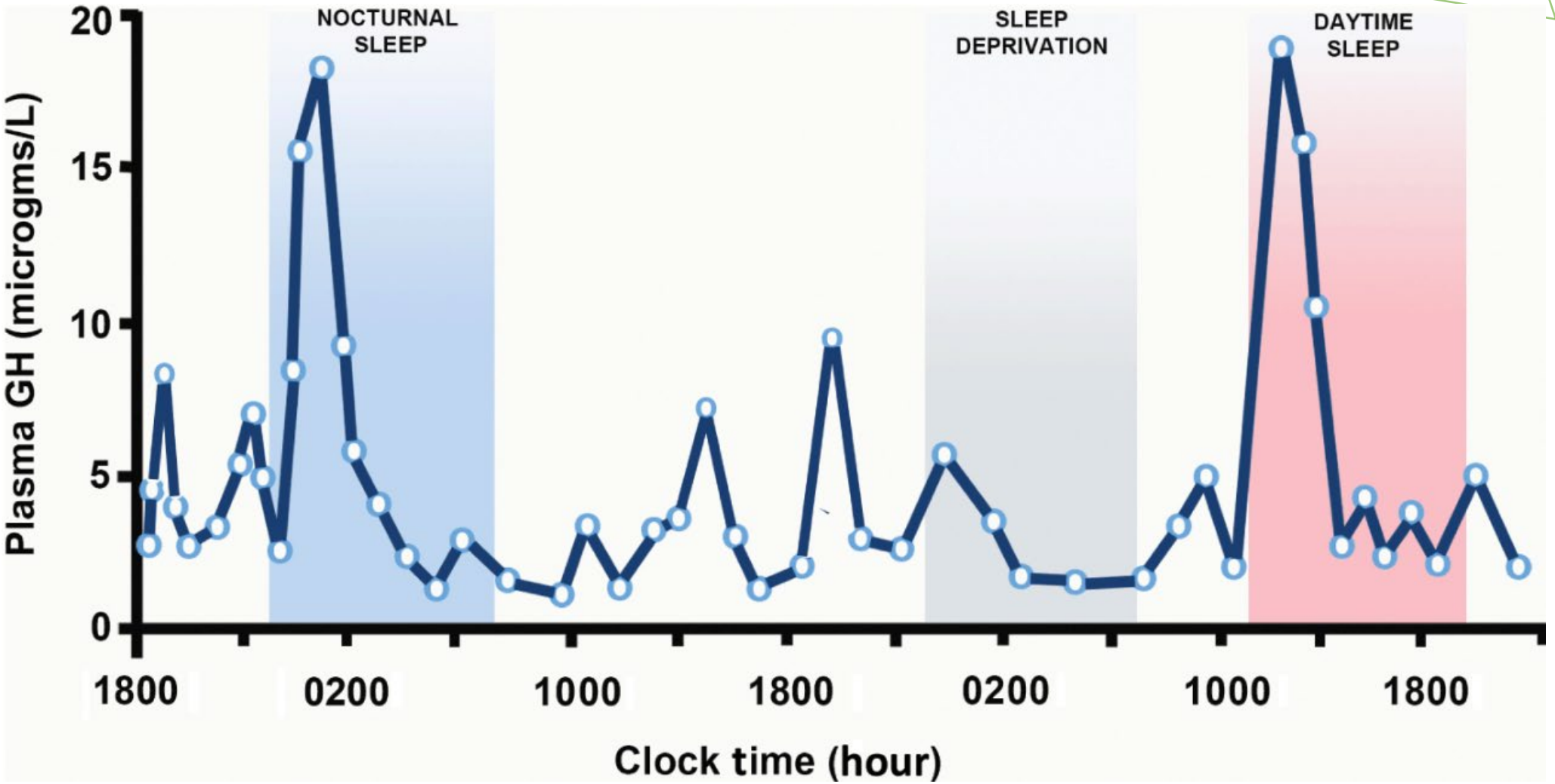
- Increase amino acid transport
- Increase nitrogen retention
- Increase lean tissue, and increase energy expenditure
- May affect muscle fiber distribution

Linear Growth

- Promotes epiphyseal growth
- "Dual effector" theory (Stimulates the differentiation of prechondrocytes, and the local expression of IGF-1 which increases clonal expansion of osteoblasts)

Adipose Tissue

- Acute insulin-like effects followed by:
- Increase lipolysis
- Inhibit lipoprotein lipase (LPL)
- Stimulate hormone sensitive lipase (HSL)
- Decrease glucose transport
- Decrease lipogenesis



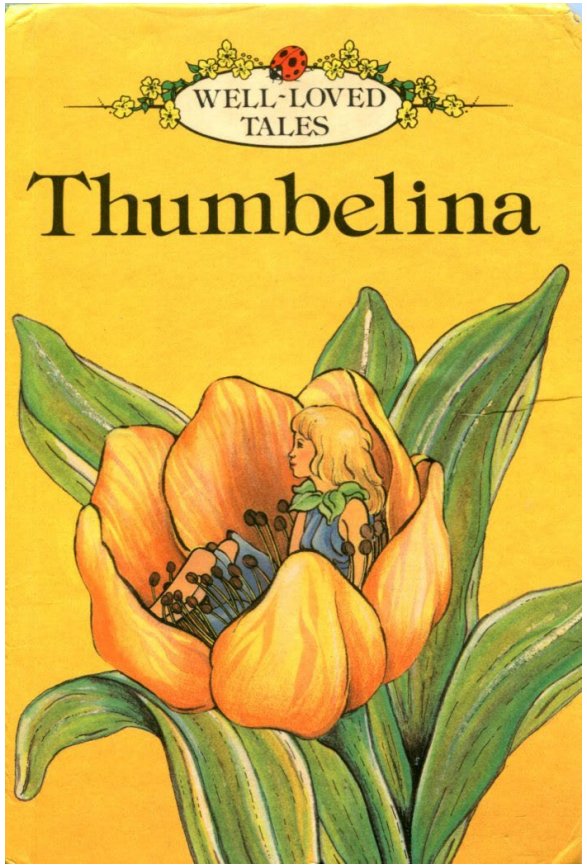
Clinical Neuroendocrinology *An Introduction*, pp. 134 – 153, 2019

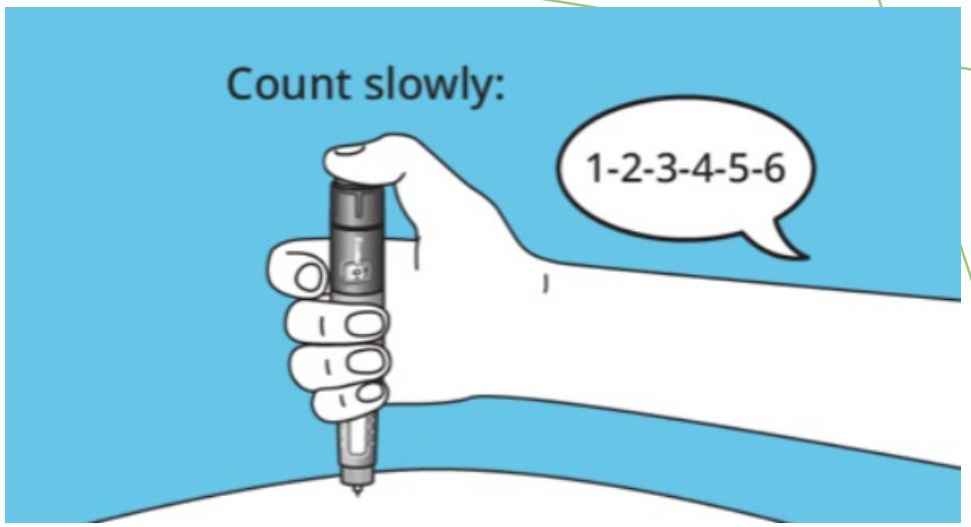
ASSESSING GH STATUS

- The generally agreed "gold standard" for assessing growth hormone is risky
  - Insulin tolerance test
- Falling height percentiles on the growth chart
- IGF-1 assays
  - Can be low in poor nutrition states or liver disease
  - Normal ranges vary by age, peak 15-19 yo and steadily decrease after 21 yo.
- GH stimulation tests
  - Stimuli (arginine, clonidine, L-dopa, glucagon) are not physiologic and are not representative of typical secretory dynamics
  - Can be influenced by age and BMI

FDA-APPROVED GH INDICATIONS

- Growth Hormone Deficiency (1985)
- Chronic renal insufficiency (1992)
- Turner syndrome (1996)
- HIV wasting enteropathy (1996)
- Prader Willi (2000)
- Small for gestational age without catch up growth (2001)
    - Russel Silver Syndrome
- Idiopathic short stature (2003)
- SHOX gene mutations (2006)
- Noonan Syndrome (2007)




Count slowly:
1-2-3-4-5-6

UPSIDES VS. DOWNSIDES

Upsides

- Metabolic benefits in those who are GH deficient
  - Improved bone density
  - Improved lean muscle mass
  - Increased lipolysis
  - Improved cognitive function
  - Improved quality of life in those who are GH deficient
- Stature in those who are not GH deficient
  - ~ 2" additional height
    - Some more, some none
  - ? Confidence
  - ? Quality of life

Downsides

- Injections (daily or weekly)
  - 1825 injections over 5 years
- Increased insulin resistance
  - Diabetes
- Increased intracranial pressure
- Disproportionate growth
- Increased risk for slipped capital femoral epiphysis (SCFES)
- Sudden death case reports in children with Prader Willi Syndrome who had sleep apnea
- Increased risk for tumors in those with a history of cancer or who have a genetic risk for cancer
- Financial costs
  - For idiopathic short stature ~ $25,000/in

WHAT ABOUT DOWN SYNDROME?

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"DOWN SYNDROME IS ASSOCIATED WITH":

- Short stature
- Increased adiposity
- Midface hypoplasia
- Decreased bone density
- Ligamentous laxity
- Decreased muscle mass
- Hypotonia
- Micropenis
- Cognitive impairment

Could growth hormone be playing a contributing role in any of these?

CAN PUBLISHED LITERATURE HELP US ANSWER SOME QUESTIONS?

PubMed Search

- ("down syndrome"[MeSH] OR "down syndrome"[tw] OR "down's syndrome"[tw] OR "trisomy 21"[tw]) AND ("growth hormone*"[tw] OR "growth hormone"[mesh] OR "igf"[tw] OR "igf1"[tw] OR "igfbp3"[tw] OR "insulin like growth factor"[tw] OR "Insulin-Like Growth Factor I"[mesh] OR "somatoKine"[Supplementary Concept])
- ~120 results
- Screened and reviewed systematically using Covidence

QUESTION 1.

Is the Growth Hormone Axis Dysregulated in Individuals with Down Syndrome?

frontiers | Frontiers in Pediatrics

TYPE Original Research
PUBLISHED 22 February 2023
DOI 10.3389/fped.2023.1132296

GHRH-GH-IGF1 axis in pediatric Down syndrome: A systematic review and mini meta-analysis

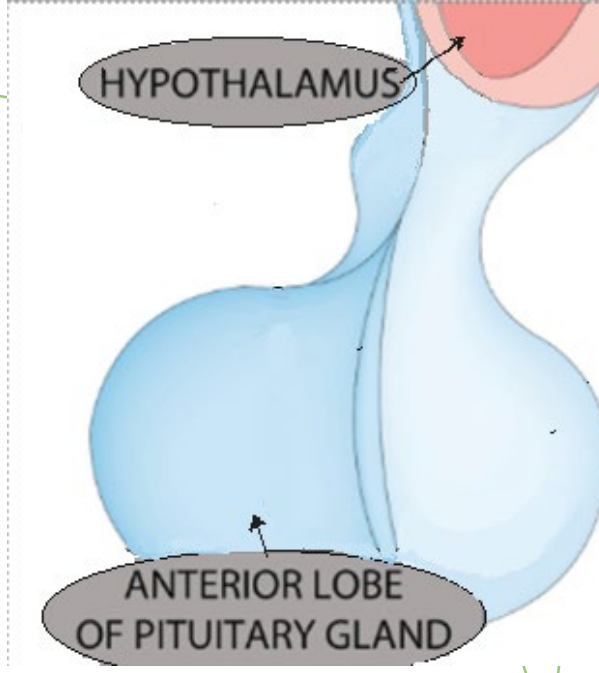
David Shaki[1,2], Eli Hershkovitz[1,2]*, Shai Tamam[3], Arkadi Bollotin[2], Odeya David[1,2], Guy Yalovitsky[2], Neta Loewenthal[1,2], Lior Carmon[1,2], Dganit Walker[1] and Alon Haim[1,2]

Literature search of "Down Syndrome" and "Growth Hormone" through 9/2022--> **281 articles**

Eligible studies included focused on the **assessment of the GHRH-GH-IGF1 axis function in pediatric patients with DS** and reported results of at least one of the following tests: GH stimulation test, 12- or 24-hour integrated GH concentration test, IGF-1 level assay, IGF-1 generation test, calculated bind GHBP (growth hormone binding protein)/ total GHBP ratio, or calculated GH Radioreceptor assay (RRA) / immunoradiometric assay (IRMA) ratio. Included comparative and single arm studies and case reports. --> **20 (of which 8 had a control group)**

Shaki et al, 2023

VARIABILITY IN FINDINGS:



In studies that tested the Growth Hormone Axis using different stim tests:

- L-DOPA: 37.5% - 61.5% had pathological results
- Clonidine: 50% - 65% had pathological results
- Arginine stim test: 0% - 25% had pathological results
- Insulin stim test: 0% - 40% had pathological results
- GHRH stimulation test (w/ and w/o pyridostigmine): 0% - 30% had pathological results

Tests that rely on hypothalamic stimulation of GHRH release more likely to be abnormal

Shaki et al, 2023

ABNORMAL GROWTH HORMONE PHYSIOLOGY

- 12- or 24-hour integrated GH concentration test: 83.3% - 100% had pathological results
- Nocturnal GH peak characteristics (amplitude, duration, and area under the curve) significantly lower for DS patients compared to the control groups
- Stimulated GH secretion in DS undergoes an accelerated age-related reduction, --> suggestive of a precocious impairment of central cholinergic activity that may cause somatostatinergic hyperactivity and reduced GH secretion.

Shaki et al, 2023; Rogers et al., 1999

ENDOGENOUS GROWTH HORMONE: REDUCED BIOACTIVITY

- Difference between IGF1 and 2 response to "endogenous" and "exogenous" GH
  - Children with DS have low IGF1 but normal IGF2
  - With arginine stim test (which causes release of endogenous GH from pituitary): abnormal rise in IGF1 seen
  - When exogenous GH is given, both IGF1 andI IGF2 rise

- The evaluation of GH by radioreceptor assay and Immunoradiometric assay revealed a reduced bioactivity of endogenous GH in those with pathlogically low IGF1 levels (compared to those with low-normal IGF1) in Barreca et al.

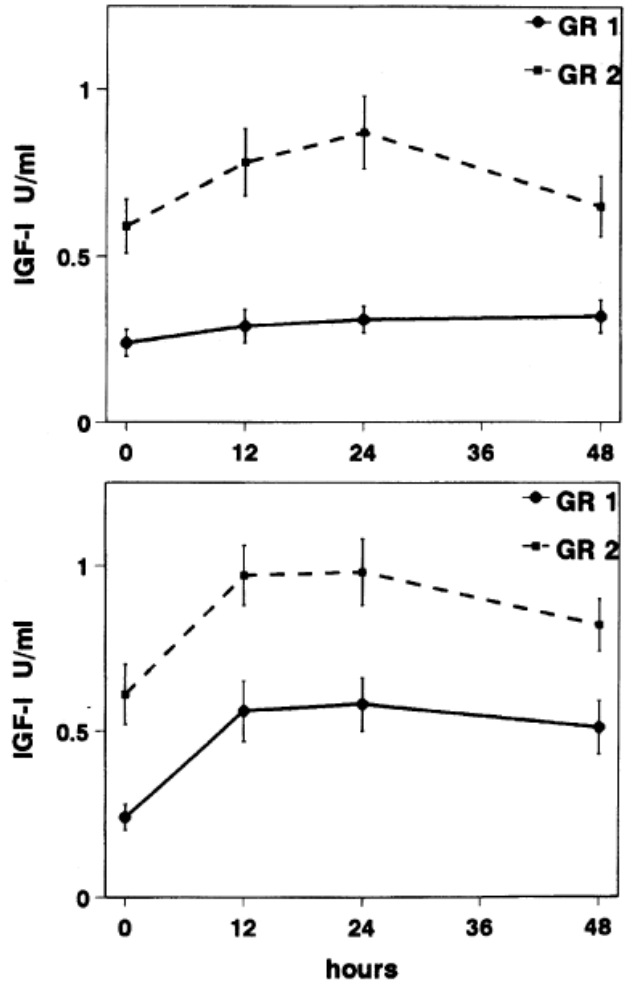


Fig. 3 - *Plasma IGF-I levels (mean±SE) after arginine (upper panel) and GH (lower panel) administration in the two groups of subjects affected by Down's syndrome.*

Shaki et al, 2023; Anneren et al, 1990; Barreca et al, 1994

IGF-1: LOW AND IMMATURE

- Barreca et al: IGF-I was significantly correlated with chronological age (N=39, 't 0.40; p=0.0004), bone age (N=26, t 0.30; p=0.024), stature (N=39, 't 0.39; p=0.004) and growth velocity (N=18, 't 0.31; p=0.05).
- Shaki et al, Meta-analysis:
  - 41% if subjects in the meta-analysis had low pathologically low level
  - 72% were under the 25th percentile
  - 87% are were under the 50th percentile.
  - More marked for those over 11.4 years: 53% with low pathological levels, 81% under the 25th percentile, and 98% under the 50th percentile.
- Conversely, IGF-2 levels are normal in multiple studies

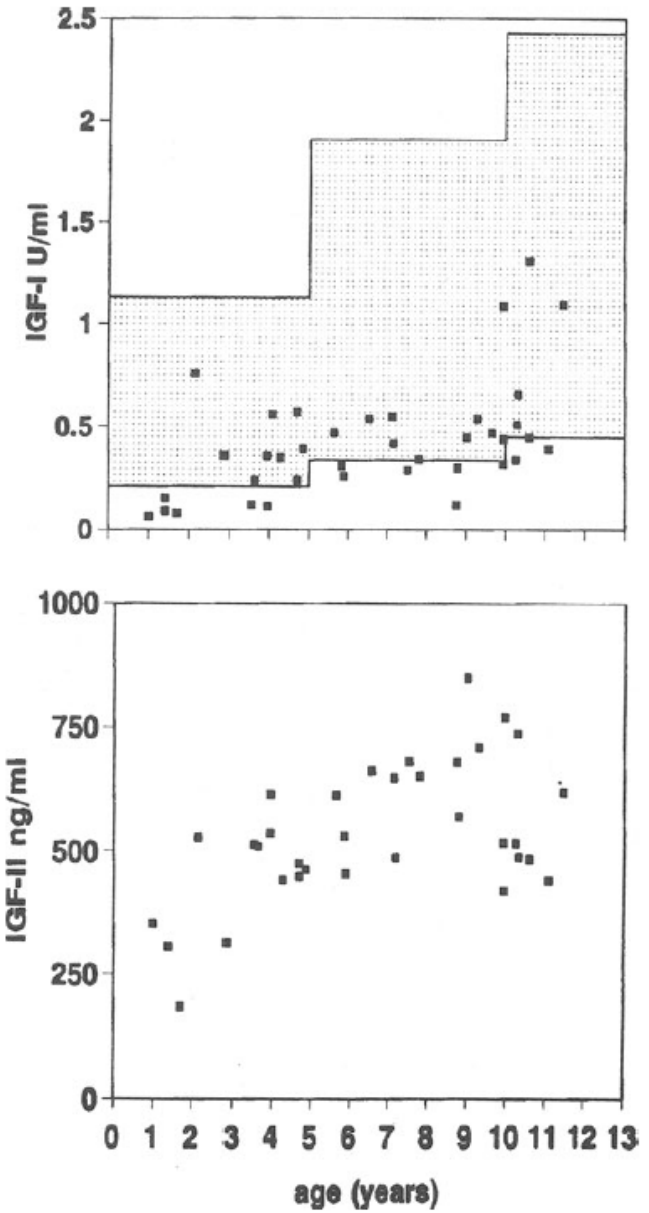


Fig. 1 - *IGF-I (upper panel) and IGF-II (lower panel) plasma concentrations in single subjects affected by Down's syndrome. The shaded area in the upper panel represents the normal IGF-I range for different age groups.*

Shaki et al, 2023, Barreca et al, 1994

DELAYED MATURATION IN IGF1

- Study of IGF pattern and the level of their receptor in fetuses with trisomy 21 and in patients with DS throughout life.
- Normal serum IGF-2 levels throughout life.
- Serum IGF-1 did not rise during childhood and remained at a low level throughout life.
- Determination of serum IGF by a radioreceptor assay (detects IGF-1, IGF-2 & fetal forms of IGFs):
  - Deficit in serum RRA-IGF in fetuses
  - Elevated levels at birth and throughout life
  - Suggests circulation of immature/fetal

Annerén et al, 1990

GROWTH HORMONE RECEPTOR - NORMAL

- Evaluation of the calculated bound GHBP (growth hormone binding protein)/ total GHBP ratio that was found to be normal and equal to controls in Barreca et al
- No differences were observed in fetal brain or liver binding sites for IGF-1, IGF-2, or insulin.

Shaki et al, 2023, Barreca et al, 1994

QUESTION 1.

Is the Growth Hormone Axis Dysregulated in Individuals with Down Syndrome? YES.

Likely hypothalamic in origin, with accelerated age-related reduction and possibly qualitative differences in endogenous GH that makes it less bioactive. Additionally, there may be incomplete switching from fetal to post-natal forms of IGF-1. Normal receptors

Wisniewski & Bobinski, 1991: Fewer neurons in the arcuate and ventromedial nuclei of the hypothalamus in patients with DS

QUESTION 2.

Is Growth Hormone Replacement/Supplementation EFFECTIVE and SAFE in patients with Down Syndrome?

frontiers | Frontiers in Endocrinology

TYPE Original Research
PUBLISHED 21 April 2023
DOI 10.3389/fendo.2023.1135768

GH treatment in pediatric Down syndrome: a systematic review and mini meta-analysis

David Shaki[1,2], Eli Hershkovitz[1,2*], Shai Tamam[3], Arkadi Bollotin[2], Odeya David[1,2], Guy Yalovitsky[2], Neta Loewenthal[1,2], Lior Carmon[1,2], Dganit Walker[1], Raphael Nowak[2] and Alon Haim[1,2]

Literature search of "Down Syndrome" and "Growth Hormone" through 9/2022-> **281 articles**

Eligible studies enrolled pediatric patients with DS who were treated with GH during childhood and examined the effect of treatment on longitudinal growth and other aspects or dealt with the ethical aspects of such treatment. --> **24**

Studies that answered one of the following two questions were included:

1) What is the effect of growth hormone treatment in children with Down syndrome? In relation to this question, studies that examined the effect of such treatment on at least one of the following six outcomes: height, head circumference, cognition and motor skills, side effects, bone age, and IGF1 level, were included. --> **16**

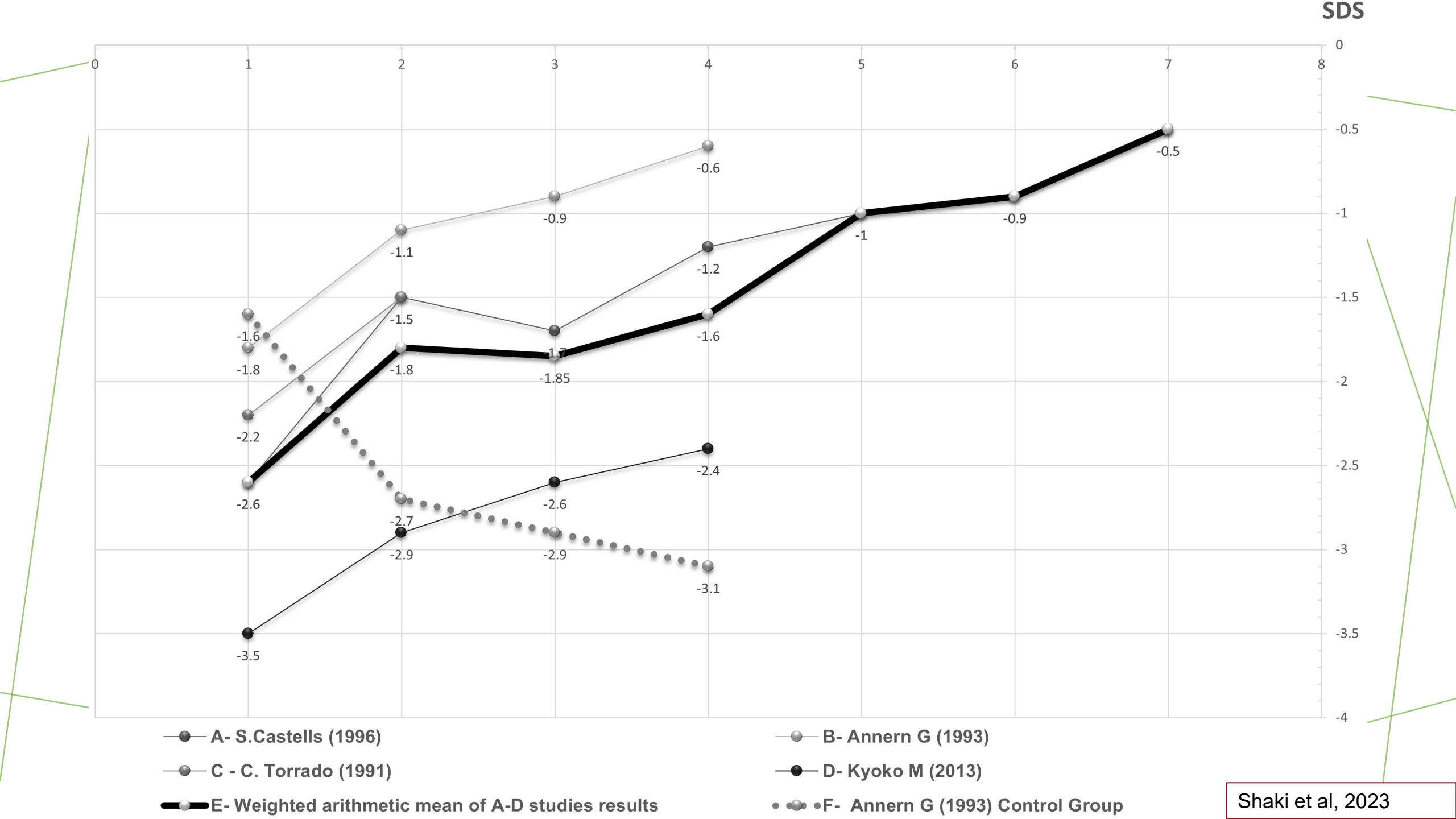
2) What are the ethical arguments in favor and against growth hormone treatment for children with Down syndrome? In relation to this question, studies that made claims in at least one of the following three categories: safety of GH treatment, necessity for GH treatment, and agreement and autonomy, were included. --> **8**

Shaki et al, 2023

META ANALYSIS SUMMARY

- Only 2 studies had a control group; specific height data for controls not available for the meta-analysis
- Not all studies required a diagnosis of growth hormone deficiency.
- Different outcomes reported:
  - Height percentiles and standard deviation scores (SDS)
  - Growth velocity (problematic because of expected variation in this parameter by age, gender, and pubertal status of the patient)
- Most studies administered growth hormone for a limited time
- **Consistent result: longitudinal growth response to GH therapy over three years of treatment in children with DS.**
- Significant difference in the change in height SDS (Means of -1.22 and 0.81, p-value<0.0001).
- In one study, the predicted adult height was calculated during therapy, and normalized in 91% of GH-treated children
- No significant difference in response to GH between children with and without proven GH deficiency (p= 0.73)

Shaki et al, 2023



Shaki et al, 2023

HEAD CIRCUMFERENCE

- All studies investigating the effect of recombinant human GH treatment in the early years of life on head circumference showed a positive effect
- The degree of impact reported ranges from very slight improvement to dramatic improvement and normalization of the head circumference.
- Speculation about significance in some articles:
  - rhGH induces an increase in nerve growth factor (NGF), insulin growth factor (IGF-1) or other neurotrophic factors in DS children causing the brain to grow
  - In experimental models, neurotrophic factors have an effect on CNS maturation, differentiation, and growth.

HGH-TREATED INFANT COHORT

- Growth hormone starts to regulate growth starting at 6-9 months of age
  - Growth velocity is most markedly reduced between 6 months and 3 years of age in DS
- 16 kids with DS (12 M, 4 F) without CHD
  - 15 age-matched kids with DS in the control (6 M, 9 F)
- Treated with hGH starting between 6 and 9 months of age (avg 7.4 months)
- Treated for 3 years with daily recombinant hGH injections
- Length/height, weight, head circumference every 3 months for the first year, then every 6 months for years 2 and 3. Growth compared to 40 kids with DS in control grp
- TSH, T4, IGFs, CBC, LFTs, creatinine and Gliadin autoantibodies every 6 months during the trial and 1 year after the end of the trial
- CSF sampling of IGF assay at the start, at 1 year and 1 year after the end of the trial.
- Treatment discontinued in 1 child due to transaminitis

Annaren et al, 1993

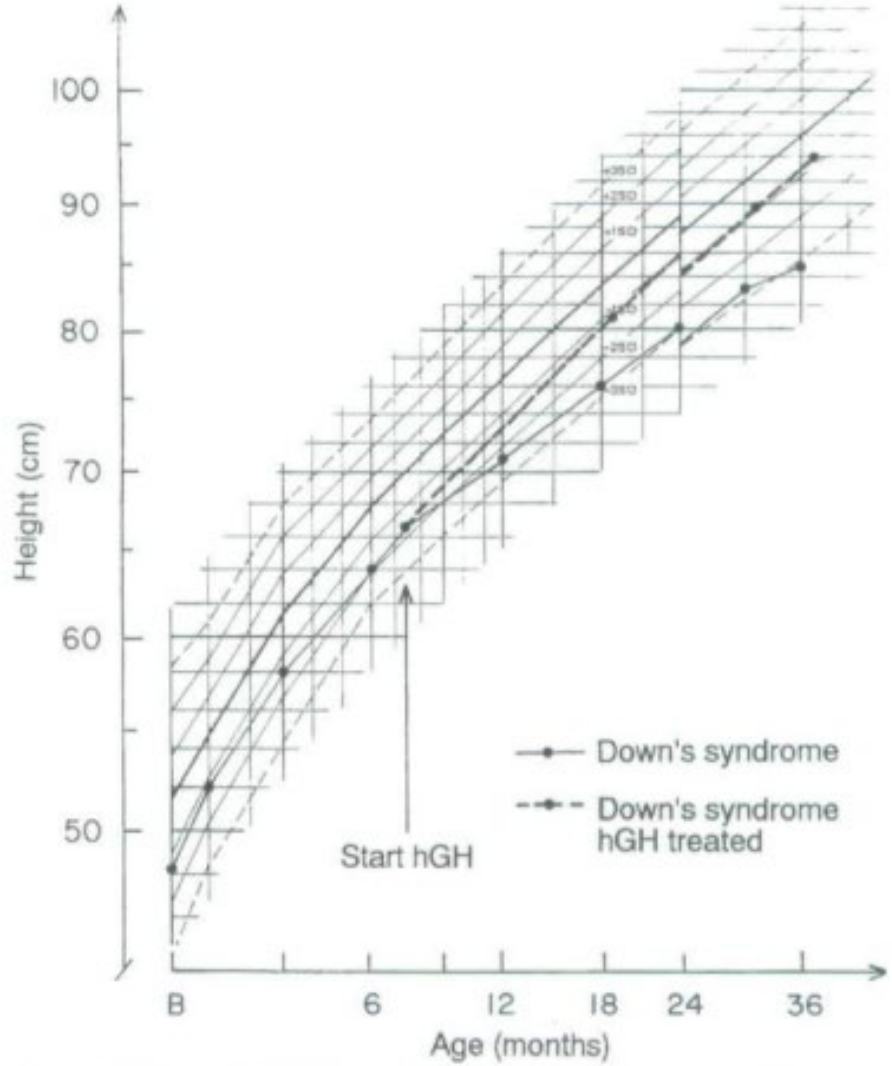


Figure 1. Mean height of children with DS treated with growth hormone (hGH) for 30 months, from the age of 6–9 months of age (mean: 7·43 months; $n=16$) compared to children with DS without hGH therapy ($n=40$). The results are plotted against the standard growth chart for healthy Swedish boys (from *Acta Paediatrica Scandinavica, Supplement* **258,** 1976).

- After 24 months of treatment all GH-treated children were above the 95th %ile for children with DS
- Bone age delayed by 6 months on average both at the start and at 1 year - increased in length not associated with increased rate in bone maturation
- 3 year follow up: Growth velocity declined after treatment stopped.

Annaren et al, 1993; Annaren et al, 1996

IMPACT ON DEVELOPMENT

- Developmental tests performed before GH treatment, after one year of treatment, at the end of treatment, and one year after treatment was stopped.
  - Motor perceptual test – motor development
  - Griffith's test – locomotor, persona-social, hearing and language, eye and hand coordination, performance/problem solving, and practical reasoning
- No differences in mental (Griffith's mental development scales) or gross motor development were observed between the control and treated groups at the age of 3.5 years—when the GH treatment was ended.
- However, a somewhat better fine motor performance ($p < 0.01$) was noted in the GH treated children.

Annaren et al, 1990

LONG TERM F/U: DEVELOPMENT

- Follow up of the cohort treated for 3 years with hGH starting between 6 and 9 months of age
  - 12 of the 16 GH-treated patients and ten of the 15 controls
- No difference in anthropometric measurements except head circumference (higher in GH grp)
- No difference in Brief IQ
- Significantly higher scores in all subtests of cognitive tests Leiter-R and WISC-III
- Some improvements in motor scores in GH group

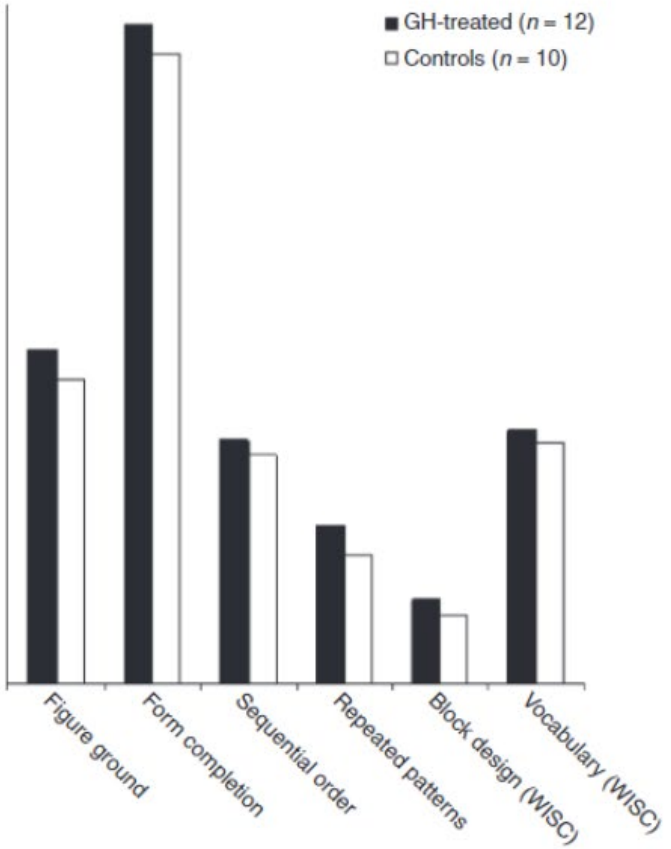


Figure 2 The figure illustrates that the mean raw point scores of the previously treated adolescents were above those of the controls in all six subtests of Leiter-R and WISC-III. The difference between the groups is significant ($p < 0.03$) in a binomial test.

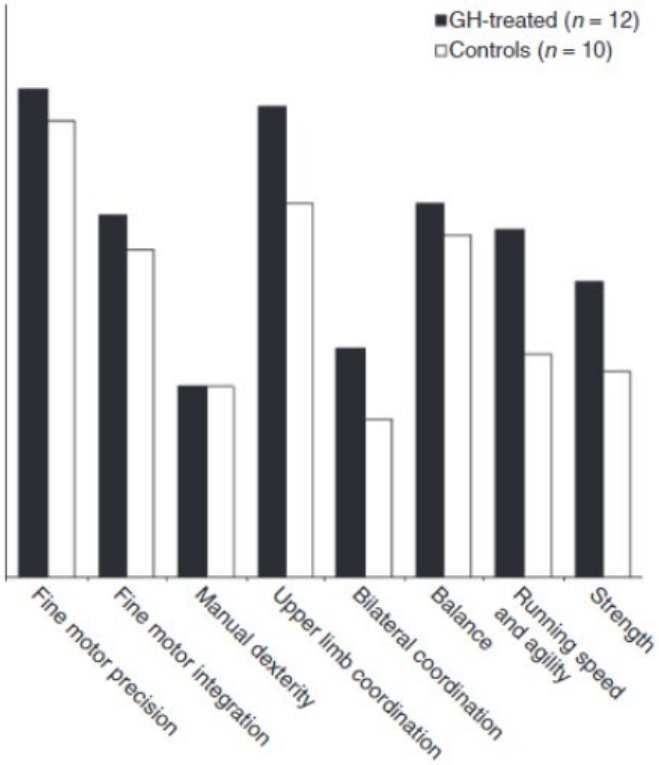


Figure 3 Illustration of the mean raw point scores of motor performance on BOT-2 for the previously GH-treated adolescents and the controls. The scores were slightly but consistently higher in the previously treated group than in the controls in all subtests but one, reaching borderline significance in a binomial test ($p < 0.07$).

Shaki et al, 2023Myrelid et al, 2010

LONG TERM F/U: HEIGHT AND LABS

- Retrospective look at growth curves and labs of 10 patients with DS (3 M and 7 F) aged between 21 and 35 years old
- Had received GH pre/peri-pubertally (mean age 9.42 years) because of significantly stunted stature and/or abnormal GH testing
- Treatment stopped after an average of 3.02 years because of (1) skeletal maturation and (2) clinical evidence of decreased height velocity
- No history of CHD or thyroid dysfunction
- Baseline bone age, TFTs, A1C, CBC with diff and LFTs. Labs repeated every 6 months during treatment.
- 10 to 15 years after the end of GH therapy, obtained TFTs, A1C, CBC with diff and LFTs.
- GH therapy resulted in an increased rate of growth and an improvement in final stature of 5.16 cm (2 inches) in males and 7.35 cm (3 inches) in females.
- No long term abnormalities in CBC, A1C, thyroid function and transaminases

Pallotti, Giuliano & Giambi et al, 2002

"CATCH-DOWN GROWTH"

- One study reported that growth velocity returned to baseline after stopping treatment
- In another study, the accelerated growth benefit was maintained short term, three years from the end of treatment, but was not maintained for the long term, ten years from the end of the treatment. Final height in those patients did not differ between the GH-treated subjects and the extended group of controls

Myrelid, 2010

CRANIOFACIAL EFFECTS

- GH deficiency associated with crowding of the teeth, delayed tooth eruption, and delayed growth of maxilla and mandible
- Infant cohort treated for 3 years starting at 6-9 months:
  - No statistically significant differences in craniofacial development

Carlstedt et al, 1990

REPRODUCTIVE HEALTH

- Ovarian dysfunction in women with Down syndrome is well documented
- GH plays a role in the regulation of ovulation and fertility: fertility is lower in women with GH deficiency, and GH receptors and GH mRNA are found in the ovary
- Cento et al, 1998: Cohort of 6 normo-ovulatory patients with DS and impaired growth (and 12 controls without DS).
- Given FSH injections +/- exogenous GH (controls only given FSH)
- Findings:
  - The ovarian sensitivity to exogenous FSH administration (measured by estradiol production) was blunted in the DS group vs control
  - GH administration was able to restore a normalization of ovarian response to an FSH challenge.
- These results could suggest that in patients with DS, a primary dysfunction of follicular maturation may occur more frequently and may lead to anovulation or impairment of luteal function.

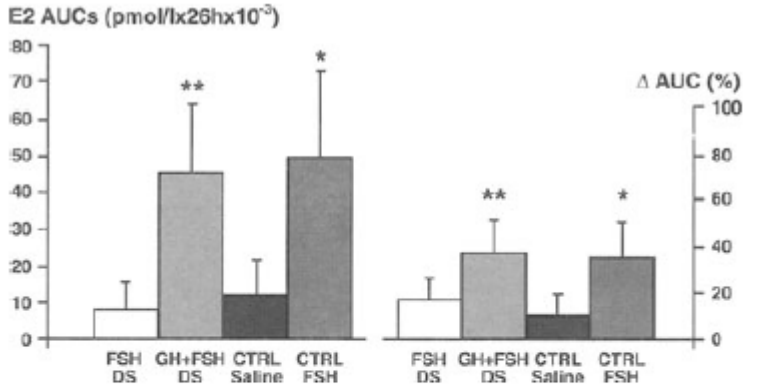


Fig. 3 - *E2 plasma concentration after pure FSH (75 IU) or saline injection in the different study groups. For other details see legend of Fig. 1. Values are analyzed as area under the 26-hour curve calculated by the trapezoidal rule; specifically results are expressed as absolute increase (Stimulated AUC) and as percent increase (Δ AUC). Conversion factor to SI units is as follow: E2= 3.671, *CTRL FSH vs CTRL Saline and FSH DS: p<0.001, **GH+FSH DS vs CTRL Saline and FSH DS: p< 0.001.*

Cento et al, 1998

SIDE EFFECTS OF CONCERN:

- Inducement of hypothyroidism (described with rhGH treatment in general population)
  - Only one child in all the studies developed hypothyroidism
- Inducement of slipped capital femoral epiphysis.
  - Not noted in the studies
- Inducement of hyperglycemia.
  - A1Cs remained stable in studies that checked it
- Possible inducement of leukemia.
  - Original concern because of cases in pts with GH deficiency treated with rhGH --> most had a hx of CNS tumor and radiation therapy
  - No cases of leukemia in any of the studies, including the 2 long term cohorts
- Possible inducement of pseudotumor cerebri.
  - One case study (Rogers et al, 1999). Child had DS + Prader Willi
- Impact of hGH on sleep apnea
  - Not appropriately evaluated in the studies

QUESTION 2.

Is Growth Hormone Replacement/Supplementation EFFECTIVE and SAFE in patients with Down Syndrome?

Effective: Yes, it's effective for height. Unclear about other outcomes

Safe: Maybe? It appears safe, but more studies are clearly needed

ETHICAL CONSIDERATIONS

- 8 publications
  - Letters to the editor, commentaries
  - Many prompted by a conference on DS and GH that took place in the early 1990s
  - A lot of the ethical discussion revolves around the **risk/benefit ratio of hGH with stature is the primary outcome**

QUESTIONS:

- Does GH dysregulation play a role in abnormal muscle physiology in DS?
- How does GH differences relate to differences in bone mass density and fracture risk in individuals with DS?
- Could GH have to do with liver dysfunction and early NASH even before transaminitis?
  - Or could liver dysfunction contribute to abnormalities in IGF-1?
- Could GH have something to do with abnormal leptin? Increased adiposity?
- How does GH dysregulation impact reproductive health?
- What role does zinc play in growth hormone dysregulation?
  - Napolitano et al, 1990
- What about the neuroprotective role of IGF-1 in ageing and dementia?
- How does this all related to interferonopathy of Down Syndrome?
  - Elevated TNF suppresses GH

HEIGHT AS A MARKER FOR MORE?

- Cross sectional study, Polish registry
- 40 children with DS 9-18 years old (median: 14.5 y/o). ~50% had CHD. 87% had hypothyroidism
- Anthropometric data (weight, height) and IQ testing with Stanford Binet-V
- Full-scale, verbal, and nonverbal IQ correlated with height percentile (P=0.03, P=0.02, and P=0.04, respectively), but not with weight or BMI
- In multiple linear regression analysis, height percentile remained as an independent determinant of the IQ results after adjusting for birth weight, hypothyroidism with L-thyroxine replacement therapy, and congenital cardiac defect (β=0.48, P=0.018)
- Note: the majority of participants obtained the lowest score for all five factors on the SB-V

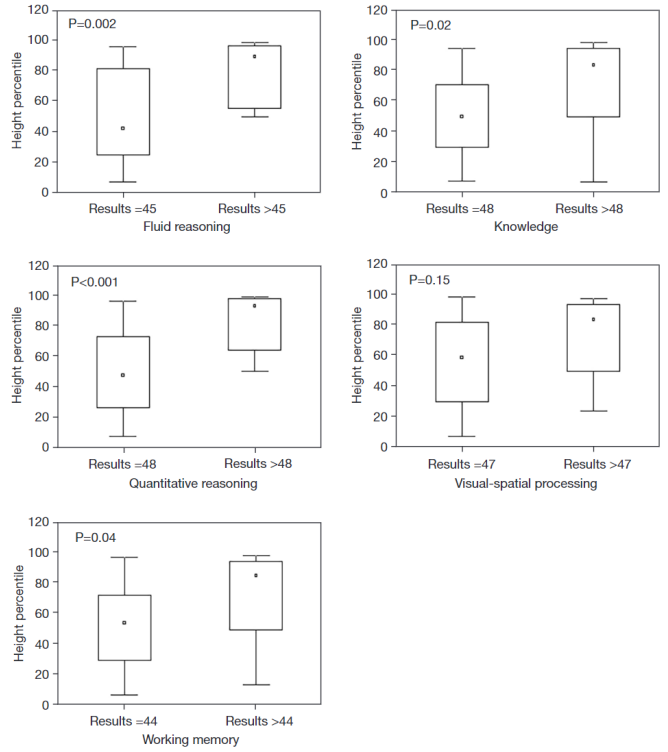
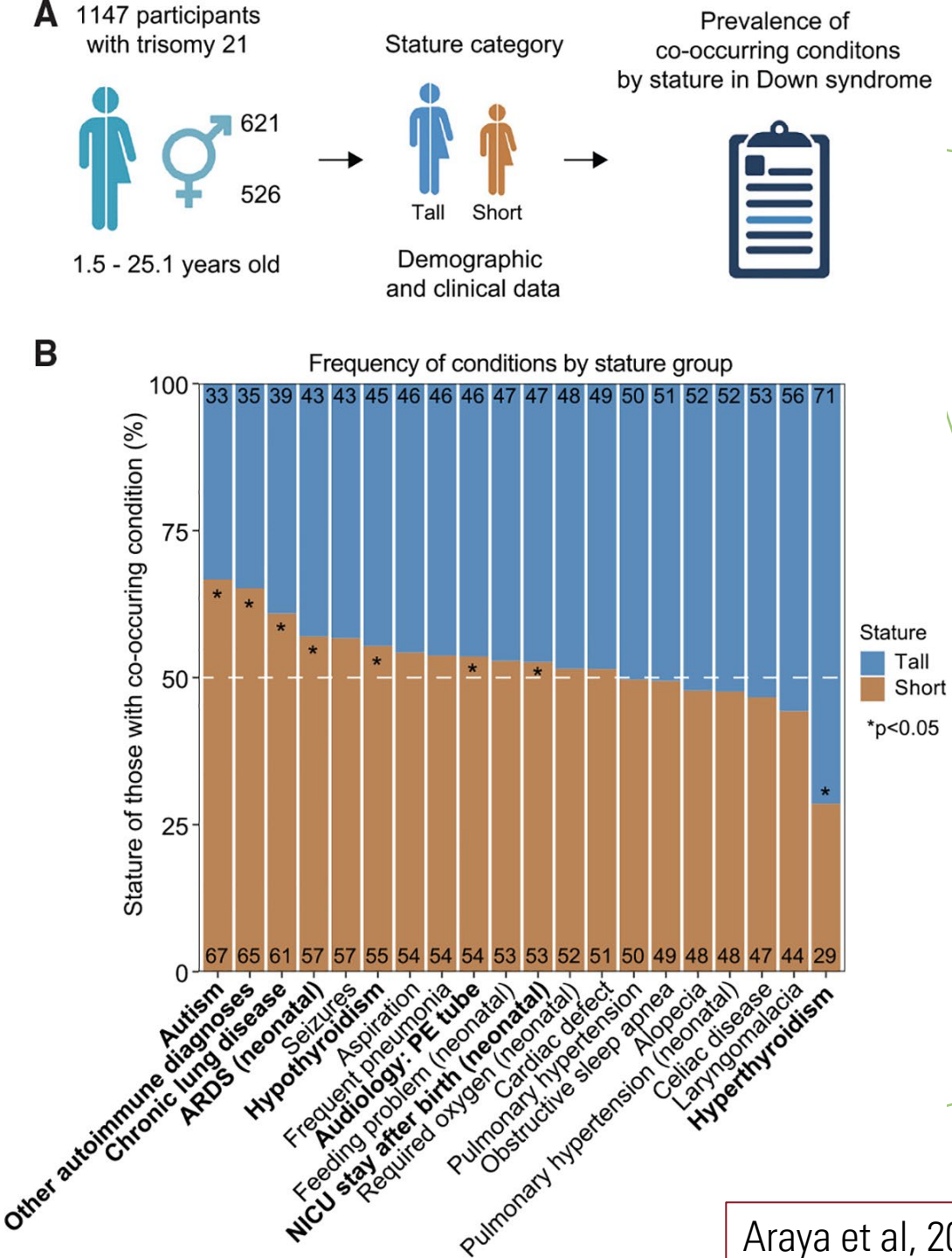


Figure 1 Height percentile of children who obtained the lowest score in the psychological test and those who obtained higher scores.

Kłosowska et al, 2022

HEIGHT AS A MARKER FOR MORE?



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PARTING THOUGHTS

- Down syndrome is a complex condition and there is no one "silver bullet" for preventing or treating associated medical and neurodevelopmental conditions.
- Individuals with DS are shorter than the general population and their growth hormone physiology is abnormal
- hGH replacement appears safe in smaller studies. It has a documented positive effect on height, with possible effects on head circumference and development/cognition
- Growing evidence of IGF-1 playing an important neuroprotective and anti-inflammatory role
- We need an appropriately powered randomized control trial that answers outstanding questions of effectiveness (beyond height) and safety
- I think we have equipoise

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