SHORT STATURE

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GROWTH

Genetic Factors

- Single Gene Disorder VS Polygenic
- Mid parental height = Target height

Boy (Fa + MO + 13) ÷ 2 = ± 8.5 cm

Girl (MO+ Fa - 13) ÷ 2 = ± 8.5 cm

GROWTH

Hormonal

Positive : GH, Thyroxin,Estrogen,Androgen

Negative: Excess Steroid

Nutritional

GH Resistance in malnutrition

Chronic Diseases

Chronic renal failure

SHORT STATURE

- Defined as height < 3rd ile for age and sex

percentile	SDS
3rd	1.9
2.5th	2
1st	3

Growth Velocity

- The fastest growth occurs in uterine life
- Peaks around 4th month of gestation GV = 2.5 cm /Wk (130 cm / Y)
- Slows down till birth
- The second acceleration takes place at puberty

Growth Velocity

- Girls have their peak growth velocity (9 cm / y) during early puberty and before menarche (Tanner II – III)
- Boys have their peak growth velocity (10.3 cm / y) during mid puberty (Tanner III – IV)
- Boys' pubertal growth spurt period is longer than girls

- Growth velocity (cm / year)

Age	Normal GV (cm)	Abnormal GV (cm)
1st Year	25.4	<16
2nd Year	12.7	<10
2 – 5 years	6.4	< 6
5 y – adolescence	5 - 6	<5
Adolescence	10 -12	--

SHORT STATURE

- Intrinsic to Growth Plate
- Chromosomal Disorders

  Down & Turner's syndrome
- Skeletal Dysplasia
- Dysmorphic Syndromes

  Russell Silver, Seckle, PWS, Bloom

  …..etc

SHORT STATURE

- Extrinsic to Growth Plate

  Endocrine causes

- GH deficiency / Resistance
- Thyroid hormone deficiency / Resistance
- Cushing's syndrome
- Pseudo hypoparathyroidism

SHORT STATURE

- Systemic Diseases
- Malnutrition with 2ry GH Resistance
- Primordial ---- IUGR
- Psychosocial Deprivation
- Idiopathic ---- - (ISS)
- Constitutional Delay (CDGP)

MEASURMENTS

- 0 - 2 years: Recombinant Length
- > 2 years : Standing Height

  Morning Multiple Positioning

  with carefulness, still error ~ 0.3 cm
- Growth Charts

  Data From North American Children

  ? To apply for other racial back grounds

MEASURMENTS

- Diurnal variation
  - Children shrinks 1.5 cm - 3 cm
  - Maximal shrinks happen 09.00 - 13.00
  - Minimal shrinks after 13.00 - end of day
  - Tallest after a wakening up from sleep
    (Morning or afternoon nap)
- Stretched / Outstretched measurements

INVESTIGATIONS

- Bone age
- TFT
- Karyotype in girls
- FBC, ESR
- Electrolytes , BUN , Creatinine
- Urinalysis and stool analysis
- Anti Endomysial Antibody

Bone Maturation

- Helpful in differentiating the types of short stature
- The two most common methods are: Greulich and Pyle (GP) = USA

  Tanner – Whitehouse (TW2) = U.K
- GP depending on Atlas comparison
- TW2 depending on score system of (20)
- TW2 is more sensitive & more time consuming

Predicted Adult Height (PAH)

Three popular methods

1. Bayley – Pinneau : based on GP method (correlates very well > 9 y)
2. Tanner – White house: based on TW2 method
3. Roche – Wainer – Thissen (RWT) All depends on accurate BA readings

GH Testing

- Screening tests
  - IGF-1, IGFBP3
    (Neither are completely sensitive or specific)
  - Exercise GH level ± propranolol
- Stimulation tests

  Should be two pharmacological tests

Stimulation tests

- Physiologic
  - al Sleep
  - Exercise
- Pharmacological
  - Arginine
  - Glucagon
  - Clonidine
  - L-Dopa
  - Insulin
  - GHRH

Sex-Steroid Primed test

- To differentiate CDGP from GHD
- Controversial issues between endocrinologists (to do or not !!)
- Useful in prepuberal boys > 11 years and girls >10 years
- In boys to give testosterone 50 mg IM 3-5 days before GH testing
- In girls to give Ethinyl Oestradiol 20 mcg /day 3-5 days before GH testing

Criteria for GHD

- Height ≤ 3 % ile
- GV ≤ 4 cm / year (prepubertal)
- Exclusion of other causes
- BA ≥ 2 years behind CA
- Low GH peak following stimulation test
- Low IGF-1 & IGFBP-3
- Increased growth rate after exogenous GH treatment

GH Treatment

Five FDA Approved Indications

- GHD in Children (Idiopathic / 2ry)
- GHD in Adults
- CRF - Pre transplant
- Turner's syndrome
- HIV – wasting syndrome

GH Treatment

- GHD
- Growth retardation due to intracranial lesions or intracranial irradiation
- Neonatal hypoglycemia
- Turner syndrome
- CRF
- SGA (didn't catch up growth by 2 years of age)
- Precocious puberty

GH Treatment

- Relative indications
- Skeletal dysplasia: Achondroplasia
- Syndromes: Prader willi, Russell silver, Noonan's,….etc.
- IUGR
- Glucocorticoid – induced short stature

Growth Hormone Replacement

- Improves linear growth
- Body composition changes producing a reduction in total and visceral fat and increase in lean body mass
- Improvement in CV function and lipids
- Improves Quality of life
- Increases bone mineral density
- Improves memory, alertness, and concentration

- GH administration improves growth rate, suggesting the so-called pulsing message of GH to its target cells.
- Nocturnal administration mimics physiological GH secretion may add to efficacy.
- The effect of GH wanes with time.
- First year of treatment usually produces the greatest growth increment .
- Seasonal variation in growth rate during GH therapy, with peaks in the summer and nadirs in the winter has also been described.

GH Therapy

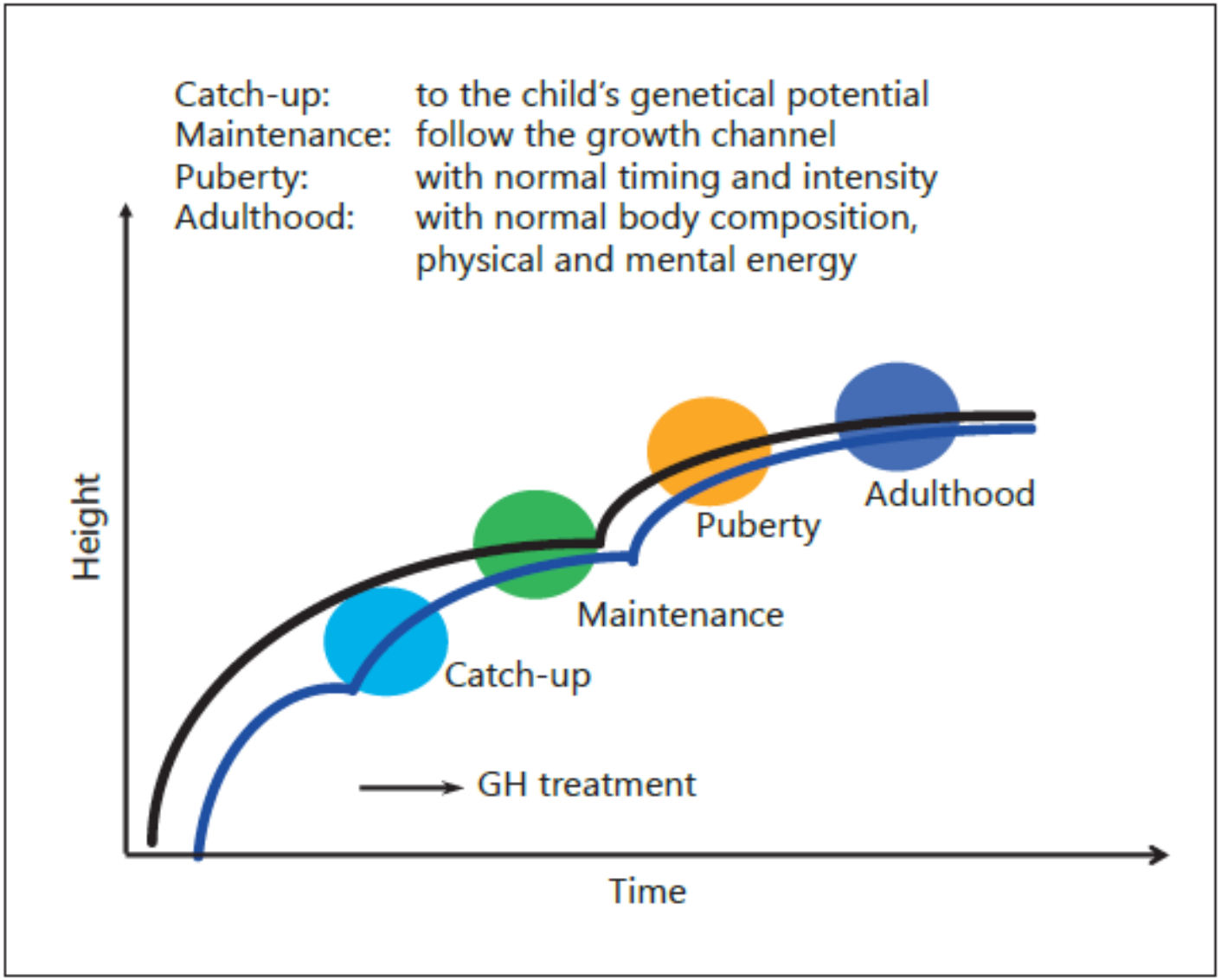
- Children treated with GH may experience transient or persistent declines in serum thyroxin (T4) levels
  - –in approximately 25%, T4 levels become abnormally low and may impair response to GH
  - –Thyroid function tests should be monitored periodically (especially early) during GH therapy to ensure detection of secondary T4 deficiency and prevent this treatable cause of a poor response to GH
- Cortisol supplementation may also impair the growth response to GH; as little as 7.5–10 mg/day of hydrocortisone may be growth-suppressive in a school-aged child
- When ACTH deficiency has been documented, the dosage of daily cortisol replacement therapy should be reduced to a level sufficient to prevent symptoms of fatigue and lack of energy

Year of initial FDA approval	Indications for GH treatment
1985	Pediatric growth hormone deficiency
1993	Growth failure secondary to chronic renal failure up to the time of renal transplantation
1996	Adult growth hormone deficiency
1996	HIV wasting in adults
1996	Turner syndrome
2000	Prader-Willi syndrome
2001	Small for gestational age
2003	Idiopathic short stature
2003	Short bowel syndrome
2006	*SHOX* gene deficiency
2007	Noonan syndrome

Hormone Therapy FDA indications of Growth

- Growth hormone deficiency
- Chronic renal failure
- Turner Syndrome
- Prader-Willi Syndrome
- SGA
- Idiopathic short stature
- AIDS wasting
- Noonan Syndrome
- Chronic diseases
- Skeletal dysplasia (Achondroplasia)
- Others

Targets of GH Therapy



Albertson Wikland, Horm Res 2012

Effects of GH Therapy in Children

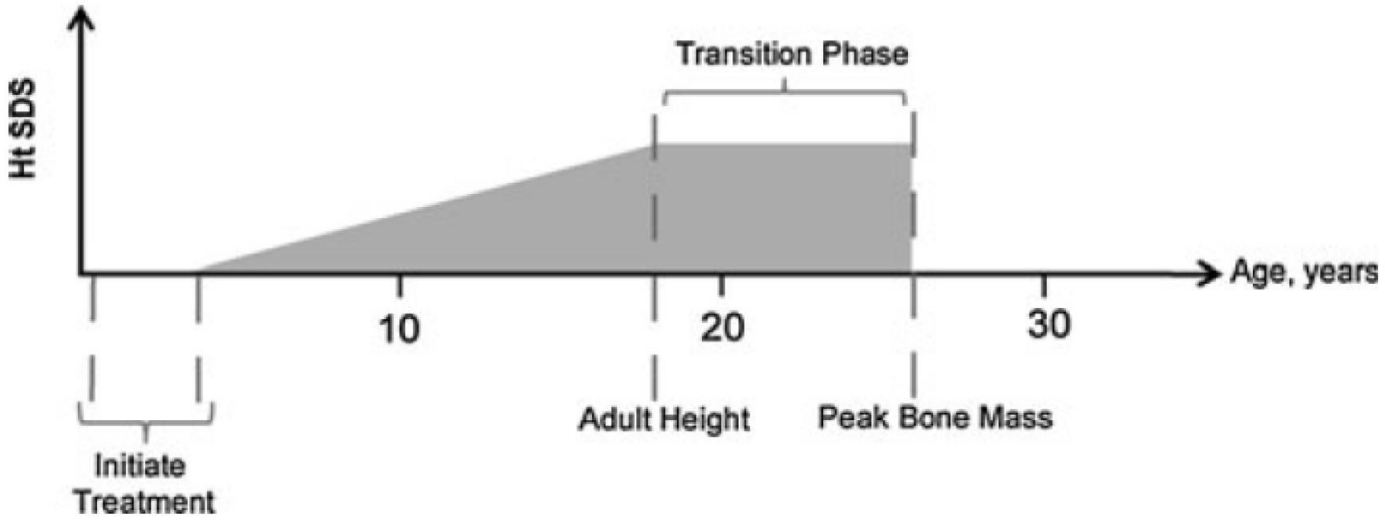


Fig. 1 Outcomes of growth hormone (GH) treatment for patients with GH deficiency (GHD). After initiation of treatment, prepubertal children show increases in height SD score (Ht SDS) over time. GH treatment is usually terminated when adult height is attained (normally in late adolescence to early adulthood). Patients with reconfirmed GHD may continue GH therapy. Peak bone mass is usually attained by approximately 25 years of age

Cook DM et al, Pituitary 2012

GH Therapy

- The recommended GH dose is calculated based on body weight & vary according to specific condition (i.e. dose of GHD is different from that of CRF or ISS).
- In case of GHD, treatment with GH should be initiated early & be monitored by a pediatric endocrinologist every 3–6 months in order to:
  - –verify growth velocity.
  - –identify possible side effects.
  - –titrating the GH dose by measuring IGF-1 & using prediction modules !!).
  - –Checking for patients compliance (adherence).

Glucocrticoid Induced Short Stature

- Mechanisms

- Promoting protein catabolism
- Inhibiting collagen synthesis
- Impairing the action of IGF-1
- Suppressing endogenous GH secretion through augmentation of hypothalamic somatostatin tone

GH Treatment

- Starting dose 35-50 microgram/kg/day or 14 – 22 iu / m^2 / wk s.c 6 or 7 days / week

When to stop treatment

1. Not responder: GV has not reached 50^{th}% for BA after 6m of treatment
2. BA > 15.5 for boys, > 13.5 for girls
3. When boys reach Ht = 169 cm, girls Ht = 156 cm (10^{th} % of adult height)

Safety of GH

- Leukemia: No supporting data
- Acute Pancreatitis
- Prepubertal gynecomastia
- Glucose intolerance and insulin resistance
- Benign intracranial hypertension
- Slipped capital epiphysis

Safety Of GH

- Hypothyroidism in GH deficient after starting replacement
- Worsening Scoliosis
- Neutralizing Antibodies (GH Gene deletion)

  RX with Synthetic GHRH

  Sermorelin Acetate (Geref)