GROWTH HORMONE TREATMENT TO FINAL HEIGHT IN CHILDREN WITH GROWTH HORMONE DEFICIENCY: EVIDENCE FOR AN EARLY THERAPY INITIATION EFFECT

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Introduction

- **GH is a single polypeptide chain of 191 amino acids which is synthesized in the anterior pituitary by the somatotrope cells. It is the most abundant hormone in the pituitary accounting for 25% of the glands hormones. Approximately 75% is secreted in the 22kD form, while the remainder consists of 20kD and 17kD variants produced by alternative splicing. GH secretion is regulated by two hypothalamic hormones, GHRH and somatostatin with a stimulatory and an inhibitory effect, respectively. Ghrelin a peptide produced in the stomach acts as an appetite stimulant and stimulates the secretion of insulin, ACTH, PRL and GH. GH secretion occurs in a pulsatile fashion and in a circadian rhythm with a maximal release in the second half of the night. GH mediates its action both directly through its own receptor GHR and indirectly through the induced production from the liver and the periphery of Insulin-like Growth Factor (IGFs). IGF-I is the main effector of GH action in linear growth; in addition IGF-I and IGF-II are important growth factors involved in diverse cellular actions such as proliferation, differentiation and apoptosis. GH is important in promoting longitudinal somatic growth and regulating body composition, intermediary muscle and bone metabolism and glucose homeostasis. Some of these GH effects are direct actions whereas others are mediated via IGF-I.**

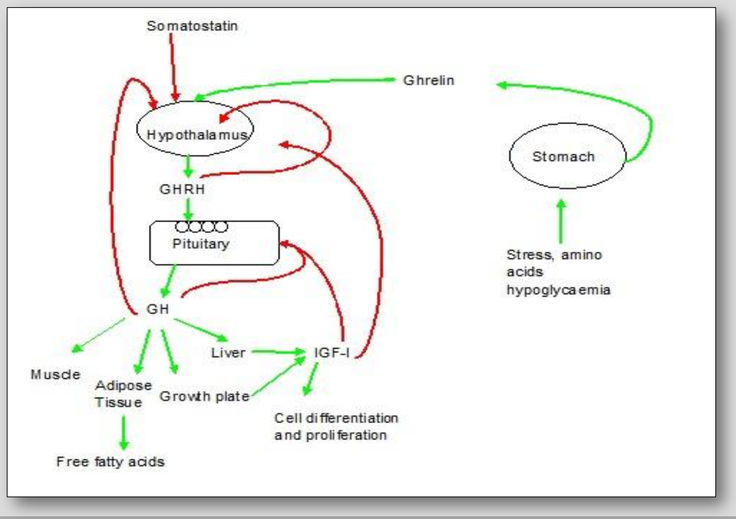
GH deficiency (GHD) can present either in isolation or in combination with other pituitary hormone insufficiencies (multiple pituitary hormone deficiency). The diagnosis of GHD in childhood is based on 1) clinical assessment 2) biochemical tests of the GH-IGF-I axis and 3) radiological evaluation of the hypothalamus and pituitary. The major clinical feature of GH deficiency is growth failure, which typically occurs after the first year of life but may be apparent earlier in severe GHD. The earliest manifestations are a reduction in height velocity followed by a reduction in height SDS adjusted for mean parental height SDS. Patients to be evaluated for growth hormone deficiency include: 1) Severe short stature (defined height >3 SD below mean). 2) Height more than 1.5 SD below mid parental height. 3) Height >2 SD below mean with height velocity over 1 year >1 SD below the mean for chronological age or a decrease of more than 0.5 SD in height over 1 year in children aged >2 years. 4) In the absence of short stature – a height velocity more than 2 SD below mean over 1 year or >1.5 SD below mean sustained over 2 years. 5) Signs indicative of an intracranial lesion or history of brain tumour, cranial irradiation or other organic pituitary abnormality. 6) Radiological evidence of a pituitary abnormality. 7) Signs and/or symptoms of neonatal GHD –reduced penile size, episodes of hypoglycemia and prolonged unconjugated hyperbilirubinaemia.

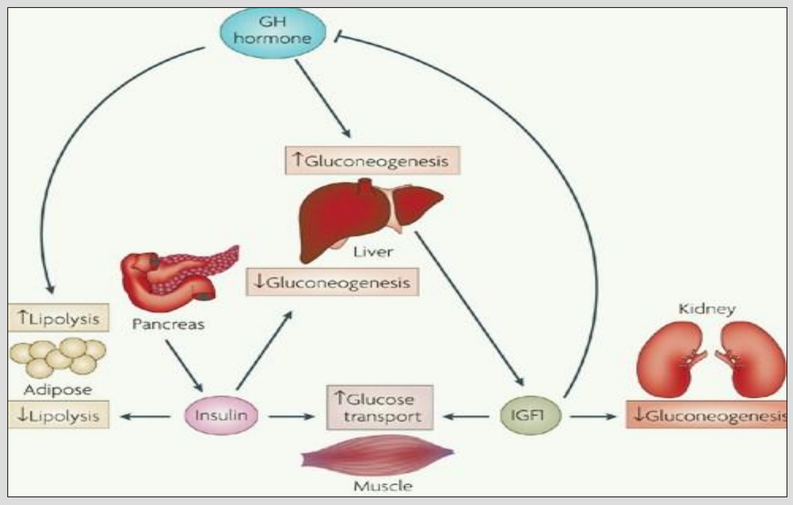
Stimulation of GH secretion

- GHRH
- Ghrelin
- Sex steroids
- Met-enkephalins
- L-dopa/clonidine
- Hypoglycemia
- Circulating amino acids
- Exercise
- Sleep

Inhibition of GH secretion

- GH and IGF-1 (negative feedback)
- Hyperglykemia
- Free fatty acids
- Glucocorticoids
- hypothyroidism





GH actions

- Longitudinal bone growth
- Anabolic effects on skeletal muscle mass
- Glucose homeostasis
- Glyconeogenesis
- Lipolytic effects
- Protein synthesis

Objective-Methods

Our objective was to evaluate the efficacy of early replacement therapy with recombinant growth hormone (rGH) in Caucasian pre-pubertal children treated for GH deficiency.

Our study included 64 boys and 49 girls, diagnosed with partial or total GH deficiency that attained their final height. None of them suffered from organic hypopituitarism. At least two standard GH stimulation assays were performed (insulin, glucagon, clonidine, L-DOPA tests) in each patient. The gold standard test is considered to be the Insulin Tolerance Test.

Inclusion criteria were : 1) Severe short stature defined as height < 3rd percentile 2) Height velocity < 3-4 cm/year 3) abnormal response at least in two standard GH stimulation tests, with peak GH < 10ng/ml.

All children had received rGH 0.11-0.17 mg/kg/W s.c. Criteria for discontinuation of treatment were bone age ≥ 14 years or height > 170cm in boys and > 165cm in girls. Boys and girls were assigned to one of four categories according to the age of rGH initiation: < 10, 10-12, 12-14 and > 14 years. Target height was predicted according to the Tanner *et al.* equation.

INHERITED DISORDERS OF THE GH-IGF-I AXIS

Genetic Disorders Causing Isolated Growth Hormone Deficiency

- IGHD type 1a (autosomal recessive) is due to mutations in the *GH1* gene, leading to a complete absence of GH
- IGHD type 1b (autosomal recessive) is due to mutations in the *GH1* gene or within *GHRHR.*
- IGHD type 2 (autosomal dominant) is caused by mutations that affect splicing of GH1, leading to impaired GH release or folding.
- IGHD type 3 is (X-linked recessive) is characterized by immunoglobulin and GH deficiency.

Genetic Disorders Leading to Abnormal Pituitary Development and Multiple Pituitary Hormone Deficiency

- Mutations in POU1F1, PROP1, HESX1, LHX3, LHX4, SOX3, SOX2, GLI2, GLI3, OTX2, FGFR1, FGF8 and PROKR2

Abnormal GH response

- Bioinactive GH with normal to high levels of GH and low IGF-I.
- Laron syndrome which is caused by loss of function mutations in the *GHR.*

GH insensitivity

- *IGF-I* mutations
- *IGF1R* mutations

ACQUIRED GH DEFICIENCY

- **Tumours of the Hypothalamus or Pituitary,** e.g. craniopharyngioma, pituitary adenomas, optic pathway glioma, germinoma
- **Radiation CNS**
- **Traumatic brain injury**
- **Hypophysitis**
- **Idiopathic**
- **Infiltrative diseases, e.g.** sarcoidosis, tuberculosis, histiocytosis X, hemochromatosis.
- **Infarction of the pituitary or hypothalamus**

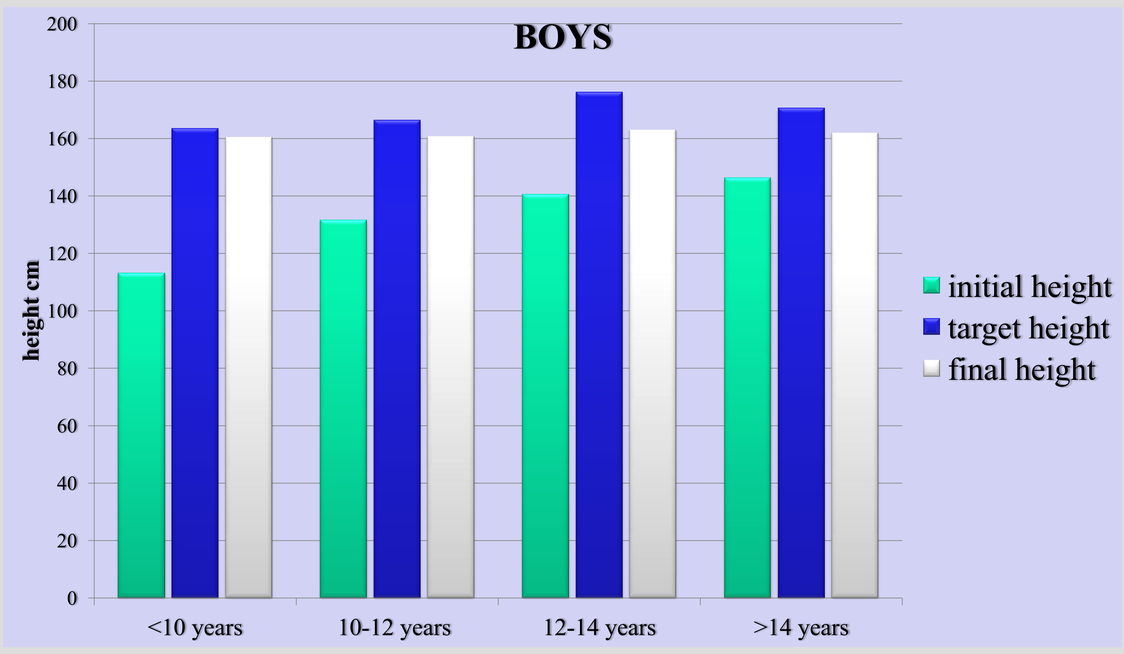
Results

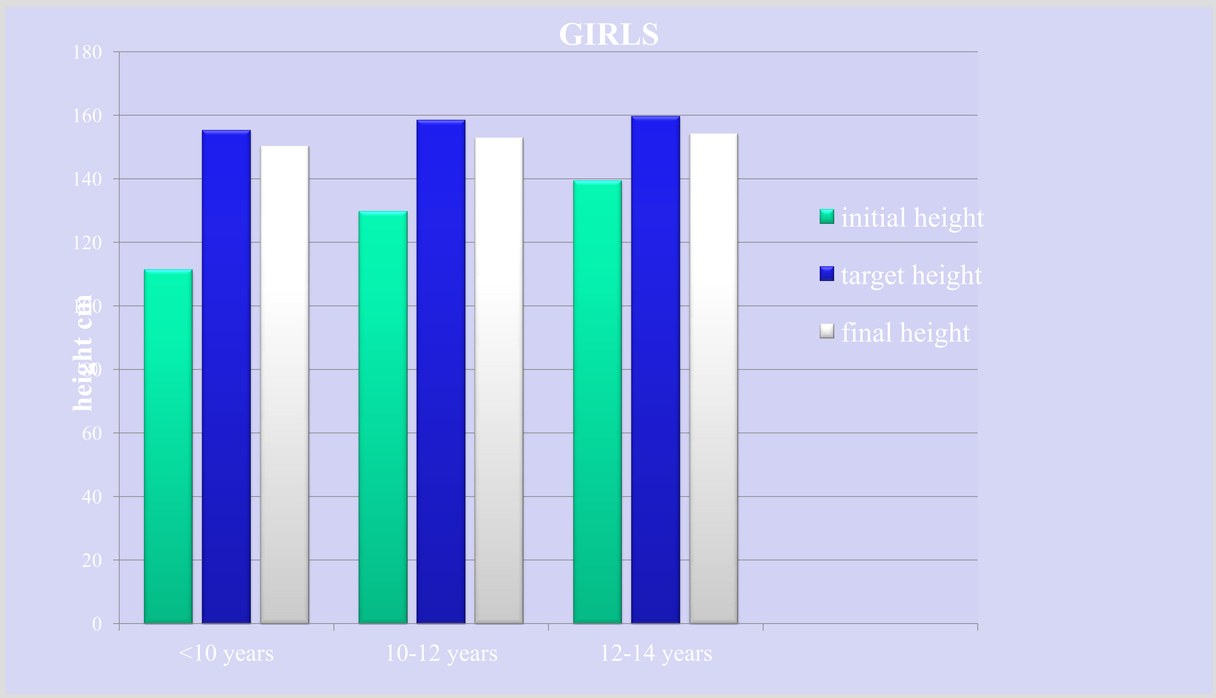
BOYS

The mean adult height in boys aged < 10 years at treatment initiation was 1.83 ±1.028 SDS (average height 160.08±5.226cm) and compared favourably to the Tanner target height, as the mean difference between final and target height was -3.22 ±6.63cm. Younger patients with marked bone age delay had better outcomes. On the contrary, for boys that aged 12-14 and > 14 years at treatment initiation, the mean final height was significantly lower than target height (mean difference -13±4cm and -8.625 ±7.360cm, respectively).

GIRLS

The mean adult height in girls aged < 10 years at treatment initiation was 1.16±0.73 SDS (average height 150.26±5.3cm), comparing favourably to the Tanner target height. On the contrary in girls aged 10-12 years at treatment initiation the mean final height was -1.02 ±0.36 SDS (152.72±2.6cm) and in girls aged 12-14 years -0.98±0.45SDS (154.18±3.58cm). The latter results were inconclusive. Thus, in the girl group, although final height measurements were within the normal adult range the results could be modified due to estrogen effects on the epiphyseal plate.





Conclusions

❖rGH in low dose schedules may have satisfying results in final adult height in boys, when they are treated early, in ages < 10 years old.

❖In girls the results are inconclusive, due to oestrogen effect on epiphyseal plate. The results could be modified if rGH is combined with GnRH analogs to delay puberty.

❖Children in early puberty need higher doses of rGH to achieve satisfactory adult height