INTRODUCTION

Longitudinal growth assessment is essential in child care, short stature can be promptly recognized only with accurate measurements of growth and critical analysis of growth data ***(Cohen et al., 2010)***. Reviewing the patient's growth chart is critical to evaluating short stature. Deviation from a prior growth pattern appropriate for the genetic background often heralds new pathology ***(Lindsay R, et al., 1994)***, short stature is defined as a standing height more than 2 standard deviations (SDS) below the mean (or below the 2.5 percentile) for sex ***(Cohen et al., 2010).***

The height of people with short stature may vary from about 81 cm (2 feet 8 inches) to 142 cm (4 feet 8 inches) ***(Collett et al., 2008)***. GHD children show slow growth that may not appear until the child is 2 to 3 years old. The child may be much shorter than most or all of the children of the same gender and sex ***(Parks et al., 2007)***.

Additionally, a child with GHD still has a normal body diameter as well as normal intelligence. However; the face often appears younger than those of the children of the same age. A GHD child should be plotted on a standardized growth chart. The child growth may range from flat (no response) to very shallow (minimal growth) ***(Parks et al., 2007)***.

Children with GH deficiency have altered body composition and tend to be obese, with an increase in central adiposity and increased body fat mass (TBF) and decreased fat-free mass (FFM) which together may impair insulin sensitivity and cause adverse metabolic effects ***(Binnerts et al., 1992).***

Ghrelin, the endogenous ligand specific for the GH secretagogue receptor, was originally purified from rat gastric mucosa ***(Kojima et al., 1999).*** It is localized throughout the gastrointestinal mucosa with the highest content in the gastric fundus ***(Date et al., 2000),*** Predominantly produced by the stomach in humans, lower amounts of ghrelin are also found in the bowel, kidney, and placenta as well as in the pituitary, hypothalamus ***(Yoshihara et al. 2002),*** pancreas, liver ***(Wang et al., 2002),*** and testis ***(Tena-Sempere et al., 2002)***. Ghrelin is the strongest releaser of GH known today ***(Arvat et al., 2002).***

It has orexigenic effects ***(Shintani et al., 2001)*** and increases food intake and adiposity in both animals and humans ***(Wren et al., 2001).*** The circulating levels increase before meals ***(Cummings et al., 2001)*** and are suppressed by the intake of nutrients, especially glucose ***(Shiiya et al., 2002).***

Ghrelin promotes glucose oxidation and lipogenesis ***(Wren et al., 2001),*** whereas GH promotes glucose production and lipolysis ***(Ottoson et al., 1995).***

AIM OF THE WORK

The aim of this work is to:

1- Assess serum Ghrelin and Glycemic profile and insulin homeostasis in growth hormone deficient children

2- Determine the effect of growth hormone replacement on their level after 9 months of therapy.

Chapter (1)

SHORT STATURE

Longitudinal growth assessment is essential in child care. Short stature can be promptly recognized only with accurate measurements of growth. It optimally defined relative to the genetic endowment of the individual, and critical analysis of growth data by comparing an individual child's height with that of a large population of a similar genetic background and, more particularly, using the mid-parental target height ***(Cohen et al., 2010).***

Reviewing the patient's growth chart is critical to evaluating short stature. Deviation from a prior growth pattern appropriate for the genetic background often heralds new pathology. In addition, analysis of the prior growth pattern helps distinguish normal growth from pathologic variants of short stature ***(Lindsay et al., 1994).*** Compared with a well-nourished, genetically relevant population, short stature is defined as a standing height more than 2 standard deviations (SD~ below the mean (or below the 2.5 percentile) for age and sex ***(Cohen et al., 2010).***

Table (1): Causes of short stature:

-**Variations of Normal**. Constitutional (delayed bone age) Genetic (short familial heights) **- Endocrine Disorders** ❖ GH deficiency * Congenital • Isolated GH deficiency • With other pituitary hormone deficiencies • With midline defects • Pituitary agenesis • With gene deficiency * Acquired • Hypothalamic/pituitary tumor • Histiocytosis X (Langerhans cell histiocytosis) • CNS infections and granulomas • Head trauma (birth and later) • Hypothalamic/pituitary radiation • CNS vascular accidents • Hydrocephalus • Autoimmune * Functional GH deficiency • Psychosocial dwarfism • Laron dwarfism (increased GH and decreased IGFl) • Pygmies (normal GH and IGF but decreased IGFl) ❖ Hypothyroidism ❖ Glucocorticoid excess • Endogenous • Exogenous ❖ Diabetes mellitus under poor control ❖ • Diabetes insipidus (untreated) ❖ Hypophosphatemic vitamin D resistant rickets ❖ Virilizing congenital adrenal hyperplasia (tall child, short adult) ❖ **Skeletal Dysplasias** • Osteogenesis imperfecta • Osteochondroplasias ❖ **Lysosomal Storage Diseases** • Mucolipidoses • Mucopolysaccharidoses	**- Syndromes of Short Stature** • Turner syndrome (syndrome of gonadal dysgenesis) • Noonan syndrome (pseudo-Turner syndrome) • Autosomal trisomy 13,18,21 • Prader- Willi syndrome • Laurence-Moon-Bardet-Biedl syndrome • Autosomal abnormalities • Dysrmorphic syndromes (e.g., Russell-Silver, Cornelia de Lange) • Pseudohypoparathyroidism - **Chronic Disease** • Cardiac disorders • Left-to-right shunt • Congestive heart failure • Pulmonary disorders • Cystic fibrosis • Asthma • GI disorders • Malabsorption (e.g., celiac disease) • Disorders of swallowing • Inflammatory bowel disease • Hepatic disorders • Hematologic disorders • Sickle cell anemia • Thalassemia • Renal disorders • Renal tubular acidosis • Chronic uremia • Immunologic disorders • Connective tissue disease • Juvenile rheumatoid arthritis • Chronic infection • AIDS • Hereditary fructose intolerance **- Chronic undernutrition** • Marasmus • Iron deficiency • Zinc deficiency • Anorexia caused by chemotherapy of neoplasms. • Amphetamine treatment for hyperactivity with decreased caloric intake.

(Styne and Glaser, 2002)

According to the National Health Service (NHS), UK, restricted growth is categorized as either:

- **PSS (proportionate short stature)**: there is less-than-normal general growth throughout the body. The trunks of adults are in proportion to their legs (trunk = abdomen and chest). The most common reason is having short parents ***(Attie et al., 1997).***
- **DSS (disproportionate short stature)**: this occurs when the joints and bones do not grow properly. The person may have a severe lack of all-over body growth, or some limbs may be shorter in proportion to the rest of their body. DSS is generally linked to a change in the genes (genetic mutation) like skeletal dysplasias ***(Attie et al., 1997).***

Chapter (2)

GROWTH HORMONE DEFICIENCY

Definition:

Growth hormone deficiency (GHD) is a failure to achieve normal GH level in response to two known provocation tests ***(Lee et al., 1990).*** The spectrum of GHD in children ranges from the complete absence of GH, resulting in severe growth retardation, to a partial deficiency, resulting in slightly short stature ***(Lee Vance et al., 1999).*** GHD has a prevalence between 1/4000 and 1/15000 ***(Vnencak et al., 1990).***

Physiological secretion of GH:

The secretion of hGH is regulated by a complex neuroendocrine control system that involves intricate relationships among its various components: the CNS, hypothalamus, anterior pituitary, target glands and peripheral tissues (Fig. 1) ***(Tanncnbaum, 1991).*** GH is a single-chain polypeptide of 191 amino acids synthesized, stored, and secreted by the somatotrophs of the pituitary in response to the secretion of growth hormone–releasing hormone (GHRH) by the hypothalamus. Somatostatin, also produced by the hypothalamus but inhibits GH release ***(Casanuevae et al., 2009)***. In addition to GHRH and somatostatin, several other factors regularly mediate GH

secretion, major stress (e.g., surgery, sepsis), fasting, sex steroids, chronic malnutrition, apomorphine and levodopa all stimulate GH secretion ***(Eastman et al., 1996).***

GH is secreted by the pituitary gland in a pulsatile fashion with discrete episodic secretory bursts occurring especially after the onset of sleep and throughout the night. GH is also secreted episodically during the day, but secretory activity, especially in prepubertal children, is lower in daytime than at night ***(Shimon et al., 1997).*** Integrated GH secretion has been found in prepubertal children and young adults between 3 and 6 ng/ml/day. It increases during puberty. The mean plasma GH concentration decreases with aging. Physiological GH concentration and GH responses to provocative stimuli are greater in females than in males ***(Champman et al., 1994).***

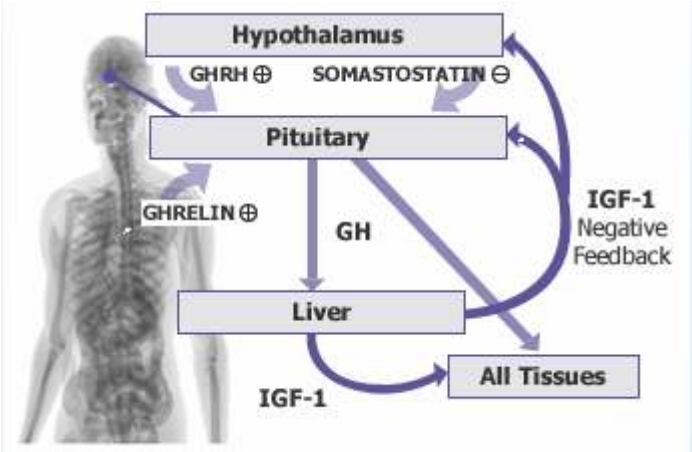

Fig. (1): Physiological secretion of GH ***(Tanncnbaum, 1991).***

Sites of GH action:

- ***Bone:***
  - 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 metabolically active 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 ostcoblasts.
- ***Adipose tissue:***
  - Increase lipolysis.
  - Inhibit lipoprotein lipase (LPL).
  - Stimulate hormone sensitive lipase (HSL).

- Decrease glucose transport.
- Decrease lipogensis.

(Aaron et al., 2000)

Aetiologv of GHD:

(1) Congenital conditions:

***A-Genetic**:*

a- Isolated GH deficiency.

b- Combined pituitary hormone deficiency.

c- Pituitary developmental defect.

B-Anatomical anomalies:

a- Pituitary aplasia.

b- Hypoplasia.

c- Stalk dysgenesis, with or without ectopic pituitary.

d- Septo-optic dysplasi..

e- Holoprosencephaly.

f- Midline defects (cleft lip or palate).

g- Encephalocele, empty sella, solitary central incisor.

(2) Trauma:

a- Accidental, including " birth injuries".

b- Surgical damage, including stalk section.

c- Child abuse syndrome.

(3) Infections and other inflammatory disease:

a- Viral encephalites.

b- Bacterial infections.

c- Fungal infections.

d- Nonspecific hypophysitis (autoimmune).

(4) Vascular:

a- Aneurysmal malformations of the pituitary vessels.

b- Pituitary infarction.

(5) Cranial irradiation:

Administered for tumors or infiltrative disease.

(6) Infiltrative disease:

a- Histiocytosis.

b- Sarcoidosis.

c- Tuberculosis.

d- Lymphocytic hypophysitis.

e- Hemochromatosis.

(7) Hypoxic insult.

(8) Toxic sequelae-of chemotherapy for malignancies.

(9) Tumors of the hypothalamus, pitutiary

Craniopharyngioma, glioma, pinealoma.

(Lee Vance et al., 1999)

Congenital GHD:

Among the congenital causes, between 5% and 30% have a familial pattern, which suggests a genetic basis**.** Known genetic causes of isolated GH deficiency include inactivating mutations in the GH releasing hormone receptor (GHRHR) gene. GHRH action is required for somatotrope proliferation (late in pituitary development) and for GH synthesis and secretion. A defective GHRHR impacts all these mechanisms, and affected patients have pituitary hypoplasia and severe isolated GH deficiency ***(Massoud et al., 1995).***

Isolated GHD, type IA:

The clinical phenotype is one of proportionate dwarfism with relative microcephaly, normal fertility, and normal lactation. Affected homozygous patients have severe GHD (termed type IA) ***(Maheshwari et al., 2003).***

Isolated GHD, type 1B:

A similar phenotype occurs with milder form (termed type IB) is seen with less disabling mutations. In type IA, secondary resistance to exogenous GH administration is seen frequently, but not always, because of the formation of high titer anti-GH antibodies to the "foreign" GH protein. Patients with type IB, on the other hand, respond well to exogenous GH because they are immune tolerant to GH ***(Maheshwari et al., 2003).***

Isolated GHD type II:

Dominantly inherited GH gene mutations (termed type II) are caused by splice site, mutations in one allele that result in skipping of exon 3, with the resultant abnormal GH protein exerting a deleterious (dominant negative) influence on the normal GH produced by the intact allele ***(Maheshwari et al., 2003).***

Isolated GHD type III:

Another type of isolated GHD that is inherited in an X-linked manner. The gene involved is unknown but resides close to the gene for 'Bruton tyrosine kinase", an enzyme that is curcial for B-lymphocyte function. Hence, this type of GHD is usually associated with hypo-or gammaglobulinemia ***(Maheshwari et al., 2003).***

Idiopathic GHD (IGHD):

IGHD is the most common form of GHD. In this type, there is presumably no organic lesion or genetic cause to explain the GHD. However, abnormalities of the pituitary gland (detected mainly by magnetic resonance imaging) are now known to be very common in patients with IGHD, but more commonly the functional defect involves the hypothalamus ***(Lifshiz and Cervantes, 1990).***

These children are proportional (i.e. having appropriate weight) with respect to length at birth. This finding indicates that these infants as a group show reduced linear growth. The aetiology may be related to a perinatal insult. There may be a history of birth trauma or abnormal birth position or presentation particularly breech position ***(Triulzi et al., 1994).***

Prader (1980) was the first to suggest birth trauma as the main cause of idiopathic GHD. Within the hypothalamic pituitary system, the somatotrophic axis reacts with greatest sensitivity to all kinds of damage. The next most sensitive function is the gonadotrophic, followed by the thyrotrophic and lastly the corticotrophic function. Whether GHD may occur alone or in association with other hormone deficiency apparently depends on the extent of the perinatal lesion ***(Van Den Broeck, 1997).***

Diagnostic approach for GHD:

1. History

Key data to obtain for the evaluation of a child with growth disturbance include the child's weight and length at birth; prior growth pattern; and the final (or current) heights and weights of parents ***(Lee et al., 2006)***.

2. Physical examination:

Endocrinologists rely heavily on accurate and reliable height assessment.

- Measure standing height in triplicate using a calibrated wallmounted stadiometer.
- In infants, length is determined in triplicate using a table top recumbent stadiometer.
- The mean value of the triplicate data serves as the true measurement.

Documenting growth velocity over time complements the initial height assessment.

- Calculate growth velocity as the change in standing height over at least 6 months (in children) or in length over at least 4 months (in infants).
- Whenever possible, obtain the original birth records to document length, weight, and fronto-occipital circumference at birth.
- Weigh all patients.
- Assessing the heights of both parents is absolutely essential. Ideally, measure each parent's height in the clinic for optimal calculation of the mid-parental target height, according to one of several formulas, among which the author prefers the following: