Assessment of Adiponectin and Glucose Homeostasis in Growth Hormone Deficient Children and Effect of Growth Hormone Treatment on Them

Thesis

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By

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Gehan Salama Reffai

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List of Abbreviations

Abb.	Full term
ADIPOR1	Adiponectin receptor
ADIPOR2	Adiponectin receptor 2
ALS	Acid-labile subunit
AMPK	AMP-activated monophosphate kinase
BMI	Body mass index
CDC	Centers for disease prevention and control
DSS	Disproportionate short stature
FDA	Food and drug administration
FFA	Free fatty acids
G/I ratio	Glucose insulin ratio
GH	Growth hormone
GHD	Growth hormone deficiency
GHRHR	Growth hormone releasing hormone receptor
GIP	Glucose-dependent insulinotropic polypeptide
GLP-1	Glucagon-like peptide-1
GLUT	Glucose transporter
HDL	High denisity lipoprotien
HSL	Stimulate hormone sensitive lipase
IFNγ	Interferon-γ

List of Abbreviations (cont…)

Abb.	Full term
IGFBP-3	Insulin like growth factor binding protein 3
IGF-I	Insulin like growth factor-I
IGHD	Isolated Growth Hormone Deficiency
IL-10	Interleukin-10
IL-1RA	Interleukin-1 receptor antagonist
ITT	Insulin tolerance test
K^+ATP	ATP-sensitive K^+ CHANNELS
LPL	Lipoprotein lipase
NHS	National Health Service
PPARα	Peroxisome-proliferator-activated receptor-α
PSS	Proportionate short stature
rhGH	Recombinant growth hormone
SDs	Standard deviations
STAT5	Signal transducer and activator of transcription
T-Cad	T-cadherin
TNF	Tumour-necrosis factor
TSH	Thyroid-stimulating hormone

INTRODUCTION

Short stature is defined as a standing height more than 2 standard deviations (SDs) below the mean for the sex and age **(Cohen et al., 2010).** Idiopathic growth hormone deficiency is the most common cause of GH deficiency (GHD) in children **(Baumann et al., 1987, 2000).**

Children with growth hormone deficiency usually present with short stature and a low growth velocity for age and pubertal stage. Alternative causes of poor growth need to be considered and excluded. Age at presentation can vary from the first few months of life to adolescence. The variability and age at presentation are highly influenced by the time of onset and the degree of GHD **(Adan et al., 1994).**

Additionally, children with GHD still have a normal body diameter as well as normal intelligence; however, the face may appear younger than those of the same age. A growth hormone deficient 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)**.

Treatment with exogenous growth hormone is indicated only in limited circumstances, and needs regular monitoring. GH is used as replacement therapy in GH

deficient children. In these patients, benefits have variably included reduced fat mass, increased lean mass, increased bone density, improved lipid profile, reduced cardiovascular risk factors, and improved psychosocial well-being **(Molitch et al., 2006)**

Adiponectin was first discovered in mice in 1995 as a transcript over expressed in adipocytes. It is also produced by other cell types, such as skeletal and cardiac myocytes and endothelial cells **(Lara-Castro et al., 2007).** Adiponectin is an insulin-sensitizing adipocytokine, replenishment of which increases insulin sensitivity in different models of insulin resistance in vivo **(Yamauchi et al., 2001).**

GH deficient children have altered body composition and tend to be obese, with an increase in central adiposity and increased intraabdominal adiposity which together may impair insulin sensitivity **(Binnerts et al., 1992)**. An inverse relationship has been shown to exist between BMI and adiponectin **(Bluher et al., 2006).**

Children with growth hormone deficiency have hyperinsulinemia, indicating insulin resistance; also have lower adiponectin levels probably due to feedback inhibition by fat accumulation **(Moller et al., 1990).**

AIM OF THE WORK

1. To assess level of serum adiponectin in growth hormone deficient children.

2. To evaluate serum adiponectin level in GH deficient children after 9 months GH therapy.

3. To assess the relation between serum adiponectin levels and growth hormone in growth hormone deficient children.

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).**