Original Article

Evaluation of left ventricular mass and function, lipid profile, and insulin resistance in Egyptian children with growth hormone deficiency: A single-center prospective case-control study

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ABSTRACT

Background: Growth hormone deficiency (GHD) in adults is associated with a cluster of cardiovascular risk factors that may contribute to an increased mortality for cardiovascular disease. In children, relatively few studies have investigated the effect of GHD and replacement therapy on cardiac performance and metabolic abnormalities that may place them at a higher risk of cardiovascular disease (CVD) at an early age. **Aim:** This study was aimed to assess the left ventricular function, lipid profile, and degree of insulin resistance in Egyptian children with GHD before and after 1 year of GH replacement therapy. **Settings and Design:** Prospective case-control study, single-center study. **Materials and Methods:** Thirty children with short stature due to GHD were studied in comparison to 20 healthy age- and sex-matched children. All subjects were subjected to history, clinical examination, auxological assessment, and echocardiography to assess the left ventricular function. Blood samples were collected for measuring IGF-1, lipid profile (Total, LDL, HDL cholesterol, triglyceride, and atherogenic index (AI), fasting blood sugar, and fasting insulin levels. In addition, basal and stimulated GH levels were measured in children with suspected GHD. **Statistical Analysis Used:** Student's *t*-test was used for parametric data, and the Mann-Whitney U-test was used for non-parametric data. **Results:** Total, LDL cholesterol, triglyceride, AI, and insulin were significantly higher in children with GHD than in healthy controls at baseline. After 12 months of GH replacement therapy, total, LDL cholesterol, triglyceride, AI and insulin were significantly decreased, while homeostatic model assessment for insulin resistance index (HOMA-IR) was significantly increased compared to both pre-treatment and control values. At baseline, the left ventricular mass (LVM) and left ventricular mass index (LVMi) were significantly lower in GHD children than in controls. After 12 months of GH replacement therapy, LVM and LVMi in GHD patients were significantly increased compared to pre-treatment values. **Conclusions:** GHD in children is associated with a significantly reduced cardiac mass and impairment of lipid profile. GH replacement therapy exerts beneficial effects both on cardiac mass and lipid metabolism by normalizing cardiac size and improving the lipid profile. On the contrary, an increase in insulin resistance is observed after 12 months GH treatment. The study suggests that children with GH deficiency should have echocardiography and lipid profile monitoring before and during treatment with GH.

Key words: Growth hormone, insulin resistance, left ventricular mass, lipid profile

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Introduction

It is now established that adults with growth hormone deficiency (GHD) may develop a cluster of cardiovascular risk factors, including unfavorable lipid profile, increased body fat, premature atherosclerosis, decreased fibrinolytic activity, increased peripheral insulin resistance,[1] as well as

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reduced cardiac performance,[2] all of which may contribute to a reduced life expectancy with an increased mortality for cardiovascular disease (CVD).[3] The existing evidence indicates that atherosclerotic CVD begins in childhood.[4] In children, obesity occurs with other risk factors for CVD, such as increased blood pressure, adverse changes in serum lipoproteins, and hyperinsulinemia, leading to acceleration of atherosclerotic lesion; therefore, the primary prevention of atherosclerotic CVD should begin in childhood. The major therapeutic role of GH in children is to promote linear growth. GH has, however, other important physiological functions in the human body influencing several key metabolic processes, body composition, muscle strength, bone mineral density, and reproductive capacity.[5] In children with GHD, echocardiographic studies of systolic function have yielded contrasting results on the effect of both GHD and GH therapy on cardiac performance.[6] On the other hand, relatively few studies have investigated the effect of GHD and GH replacement therapy on cardiac performance and metabolic abnormalities that may place them at a higher risk of CVD at an early age.[7,8] The aim of the present study is to assess the left ventricular function, lipid profile, and degree of insulin resistance in Egyptian children with GHD before and after 1 year of GH replacement therapy.

Materials and Methods

This is prospective case-control study. It included 30 children with GHD. GHD was diagnosed according to clinical and auxological criteria[9] and by peak concentration less than 10 ug/liter after two stimulation tests. In addition, 20 apparently healthy age, sex- and BMI-matched children were studied as a control. Both patients and controls were recruited from Pediatric Endocrinocriology Outpatients Clinic in Assiut University Children Hospital and the Pediatric Health insurance clinics in Assiut Governorate – Egypt. The study protocol was approved by the Ethical Committees of Assiut University Children Hospital, Egypt. Written informed consents were obtained from the parents of both patients and controls.

Inclusion criteria

- Age 4-10 years
- Height <–2 standard deviation score (SDS) (<3rd percentile)
- Idiopathic, isolated GH deficiency
- Normal thyroid function tests.

Exclusion criteria

- Any acute severe illness during the previous 6 months
- Evidence or current cardiovascular disease, respiratory, renal, liver, or endocrine disease
- Family history of atherosclerosis and cardiovascular disease
- Children with dysmorphic phenotypes, such as skeletal dysplasias or Turner syndrome
- Children on GH replacement
- Prematurity or intrauterine growth retardation
- Multiple pituitary hormone deficiency
- Children with midline defect.

Methodology

All cases were subjected to

- Full history and clinical examination including, heart rate, systolic blood pressure (SBP), and diastolic blood pressure (DPB)
- Standing height of the patients was measured using a Harpenden fixed stadiometer (Holtain Ltd, Crosswell, UK) with a sensitivity of 0.1 cm, and body weight was measured using a balance scale (SECA, Hamburg, Germany) with a sensitivity of 0.1 kg. The weight of the each subject was measured with all of the clothing removed except undergarments. Body mass index (BMI) was calculated as weight (kg) divided by square of the height (m). Target height was calculated by the method of Tanner *et al*., taking the average of mother's and father's height after addition of 13 cm in boys or subtractions of them in girls, while mid-parental height is calculated as before ±6.5 cm.[10]

Radiological examination

1. Bone age (BA) was done by performing plain X-ray left hand and wrist together with calculation of bone age SDS according to the standards of Greulich and Pyle[11]
2. Magnetic resonance imaging (MRI) of the hypothalamus-pituitary region.

Laboratory tests

All patients underwent the following tests (following not less than 12 hours fasting period):

1. Routine general laboratory tests, if needed, which include complete blood picture, renal, and liver function tests
2. Total cholesterol (normal range 100-200 mg/dl), high-density lipoprotein cholesterol (HDL-c) (normal range 30-70 mg/dl), low-density lipoprotein cholesterol (LDL-c) (normal value less than 130 mg/dl), TG (normal range 35-160 mg/dl), and fasting blood sugar (FBS) (normal range 65-100 mg/dl). Measurement was carried out using an auto-analyzer (Synchron-clinical system-CX5). The atherogenic index (AI) was calculated as the ratio of total to HDL cholesterol, considered as an index of severe cardiovascular risk.[12] Low-density lipoprotein (LDL) cholesterol was calculated using

the Friedewald formula. Fasting serum insulin measurement was done by an auto-analyzer (DDC/immulite). IR was calculated using the following equation: The homeostasis model assessment method: HOMA-IR = fasting insulin (μU/ml) × fasting glucose (mmol/l)/22.5.[13] In both children with GHD and the controls, the evaluation of these parameters was also repeated after 12 months of GH replacement therapy

3. Thyroid profile: Thyroid stimulating hormone (TSH) was estimated by immunoradiometric assay (IRMA), while FT3 and FT4 were estimated by radioimmunoassay kits from Diagnosis Product Corporation, (Los angeles, CA, USA.)
4. Stimulation of GH secretion by 2 provocation tests (clonidine and insulin tolerance test separated by 1 week interval was done. Growth hormone was analyzed by immunoradiometric assay (IRMA). The dose of clonidine given before the test was 0.15 mg/m^2 orally while that of insulin was 0.1 IU/kg i.v. In the ITT test, the blood glucose should decrease by 50% or more of the basal value or decrease to 40 mg/dl. If no hypoglycemia occurred, another dose of insulin (0.05 IU/kg) was given. With adequate hypoglycemia, peak GH levels less than 10 ng/ml indicated GHD
5. Insulin-like growth factor-1 (IGF-1) was determined at diagnosis using solid phase immunoradiometric assay (IRMA)[14] using kits from Diagnostic System Laboratories Inc (DSL)(Texas, USA).

Echocardiography

All cases and controls underwent echocardiographic studies at the time of diagnosis and 1 year after GH treatment using M-mode, two-dimensional, and Doppler techniques, using commercially available phased array system employing a 4 and 7 MHZ transducer, respectively (Magic bright 2, Vivid 3, Vingmed–Tech). Measurements were performed using the machine's incorporated analysis package. The records were made by two investigators blinded to the subjects' status. All patients were studied according to the recommendations of the American Society of Echocardiography.[15] The following measurements were taken on all patients and controls:

1. Left ventricular systolic functions:
   - Left ventricular end diastolic diameter (LVEDD), left ventricular end-systolic diameter (LVESD), left ventricular posterior wall thickness LVPWT, and interventricular septal wall thickness IVSWT
   - Percentage of fractional shortening (FS): LVFS% was calculated using the following formula 8: FS = EDD-ESD/EDD × 100.
     Where, EDD is the end diastolic diameter of the left ventricle and ESD is the end systolic diameter of the left ventricle
   - Ejection fraction (EF) was measured from the "cubed equation:
     $EF = (EDD)^3-(ESD)^3/(EDD)^3 \times 100$
   - Left ventricular mass (LV mass) and left ventricular mass index. It is performed by using LVMI calculator. The LV mass (LVM) was calculated by using Devereux's formula according to Penn's convention with the regression-corrected cube formula LVM = 1.04 $[(ISV + LVEDD + PWT)^3 - (LVEDD)^3] -13.8$ g, and expressed by LVM index (LVMi) after correction for BSA
2. Left ventricle diastolic function: Doppler studies provided indexes of ventricular filling, which were derived from the mitral flow velocity curves, i.e., maximal early diastolic flow velocity (E in cm/s), maximal late diastolic flow velocity (A in cm/s), the ratio between E and A curves (E/A, normal value >1); the isovolumetric relaxation time (IRT), which represents the interval between the end of aortic valve closure and the onset of mitral valve opening, was also evaluated.

In both children with GHD and the controls, the evaluation of these echocardiographic parameters was also repeated after 12 months of GH replacement therapy.

Treatment protocol

The Egyptian health insurance institute covers all aspect of investigation, diagnosis, and treatment of GHD in children. All patients received rhGH with a standard dose of 20 IU/m^2/week.[9] The calculated dose per week was divided for 6 days and given subcutaneously at night. The study group was followed every 3 months for anthropometric assessment, to assure compliance to therapy, to observe side-effects, and to renew the GH prescription. Compliance to therapy is continuously verified by more than one parameter e.g. height velocity, asking the parents about mode of injection and dosing, counting the empty vials, and sometimes by analysis of serum IGF-1.

Statistical analysis

Analysis was carried out using SPSS (version 16). The numerical data were represented as mean ± SD. For comparison of the two groups, Student's *t*-test was used for parametric data and the Mann-Whitney U-test was used for non-parametric data. *P* value less than 0.05 was considered statistically significant.

Results

Table 1 shows demographic, anthropometric, clinical, and hormonal parameters in GHD children and in controls at study entry. Height and serum IGF-I were significantly lower, as expected, in GHD subjects than in healthy

children ($P < 0.001$), while heart rate, SBP, and DBP were similar in the two groups.

Table 2 shows metabolic parameters in children with GHD at baseline and 12 months of GH replacement therapy and in controls at baseline and after 12 months follow-up. Total, LDL cholesterol, triglyceride, AI, and insulin were significantly higher in children with GHD than in healthy controls at baseline. After 12 months of GH replacement therapy, total, LDL cholesterol, triglyceride, AI, and insulin were significantly decreased, while HOMA-IR was significantly increased compared to both pre-treatment and control values.

After 12 months of GH replacement therapy, BMI was significantly decreased compared to pre-treatment value (16.1 ± 3.2 vs. 17.0 ± 2.8, $P < 0.05$).

Table 3 shows echocardiographic characteristics of children with GHD at baseline and 12 months of GH replacement therapy and in controls at baseline and after 12 months follow-up. LV systolic function, measured by FS and LVEF, and diastolic function, measured by E/A ratio and IRT, did not change significantly during treatment. No significant changes in cardiac size and function were observed in controls when retested after 1 year. LVM and LVMi in GHD patients were significantly increased after 1 year of replacement therapy, compared to pre-treatment values, but not significantly different compared to LVM and LVMi of controls evaluated after 1 year of follow-up.

Discussion

Our study demonstrated that LV mass and LV mass index were significantly lower at baseline in the GH-deficient group than in the control group, and that these parameters increased significantly after 1 year of GH treatment reaching values comparable to those of controls. These findings are in agreement with those reported by Shulman *et al*.,[16] in a prospective, uncontrolled, study enrolling 10 children with GHD documented a reduced LVM that significantly increased after 1 year of GH therapy. The major drawback of the study by Shulman *et al*. was the lack of a control group. In a previous short-term case-control study, Salerno M, *et al*.[17] demonstrated that heart size was significantly reduced in 30 GHD children and increased significantly after 1 year of GH replacement. Altogether, these results indicate that GH, directly or indirectly through IGF-I, is not only involved in the regulation of somatic growth in children but also in cardiac growth, probably through the modulation of the size of cardiomyocytes.[18] On the other hand, Radetti *et al*.[19]

Table 1: Demographic, anthropometric, clinical, and hormonal parameters in GHD children and in controls

	GHD *N*=30	Controls *N*=20	*P* value
Sex (male/female)	18/12	12/8	NS
Residence (urban/rural)	22/8	16/4	NS
Chronological age (year)	8.6±3.4	7.6±2.7	NS
Heart rate (bpm)	86.2±13	84.0±11	NS
SBP (mm Hg)	92.6±19	96.9±21	NS
DBP (mm Hg)	57.2±9.5	63.2±12	NS
Bone age (yr)	6.6±0.5	8.1±0.6	<0.01
Height (SDS)	−5.3±0.2	−0.8±0.1	<0.001
Height (cm)	112±11.9	131±12.12	<0.01
BSA (m^2)	0.9±0.04	0.88±0.06	NS
Body mass index (kg/m^2)	17.0±8.6	16.2±5.8	NS
GH peak at insulin (ug/liter)	3.7±0.5	-	-
GH peak at clonidine (ug/liter)	4.4±0.7	-	-
IGF-I (ng/ml)	96±12.8	132.22±10.5	<0.001

Quantitative variables are expressed as mean±standard deviation, GHD: Growth hormone deficiency, NS: Non-significant result, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, SDS: Standard deviation score, GH: Growth hormone, IGF-1: Insulin-like growth factor-1, BSA: Body surface area

Table 2: Metabolic parameters in children with GHD at baseline and 12 months of GH replacement therapy and in controls at study entry and after 12 months follow-up

	Baseline	1 year	P^1	P^2	P^3
Total cholesterol (mg/dl)					
GHD	173.3±25.4	132.7±24.2	<0.001	<0.001	NS
Controls	133.1±11.1	137.2±44			
Triglyceride (mg/dl)					
GHD	82.3±15.8	63.1±13.7	<0.001	<0.05	NS
Controls	59.2±12.1	60.2±9.4			
LDL-c (mg/dl)					
GHD	106.4±22.2	83.3±20.6	<0.001	<0.01	NS
Controls	81.3±11.1	84.2±10.9			
HDL-c (mg/dl)					
GHD	52.2±8.4	51.0±8.3	NS	NS	NS
Controls	48.4±4.6	49.8±2.6			
AI (total/HDL cholesterol)					
GHD	3.5±0.4	2.4±0.2	<0.01	<0.01	NS
Controls	2.5±0.3	2.3±05			
Fasting glucose (mg/dl)					
GHD	87.8±7.5	97.5±8.5	NS	<0.05	<0.05
Controls	86.3±6.6	83.3±2.4			
Fasting Insulin (μIU/ml)					
GHD	6.4±2.9	12.3±7.6	NS	<0.05	<0.01
Controls	6.1±1.7	5.9±3.2			
HOMA-IR					
GHD	1.40±0.66	2.99±0.21	NS	<0.001	<0.001
Controls	1.23±0.588	1.33±0.14			
BMI					
GHD	17.0±2.8	16.1±3.2	NS	<0.05	NS
Controls	16.2±3.1	16.3±2.1			

NS: Not significant, P^1 GHD patients at baseline vs. controls, P^2 GHD patients at baseline vs, 1 yr of GH therapy, P^3 GHD patients after 1 yr of GH treatment vs. controls, GH: Growth hormone, GHD: Growth hormone deficiency, HOMA-IR: Homeostatic model assessment for insulin resistance index, HDL-c: High-density lipoprotein cholesterol, LDL-c: Low-density lipoprotein cholesterol

Table 3: Echocardiographic characteristics of children with GHD at baseline an d 12 months of GH replacement therapy and in controls at study entry and after 12 months follow-up

Echo	Baseline *N*=30	After one year *N*=20	*P*[1]	*P*[2]	*P*[3]
LVEDD (mm)					
GHD	34.0±2.4	40.9±3.6	<0.01	<0.01	NS
Controls	39.9±1.1	40.7±1.2			
LVESD (mm)					
GHD	22.3±1.4	22.4±3.4	NS	NS	NS
Controls	23.8±2.7	24.5±4.2			
EF (%)					
GHD	66.2±9.2	64.9±4.9	NS	NS	NS
Controls	65.4±8.3	66.4±5.5			
FS (%)					
GHD	40.1±7.3	41.5±7.1	NS	NS	NS
Controls	40.8±8.8	39.8±1.3			
IVSWT (mm)					
GHD	3.5±0.4	4.1±06	NS	NS	NS
Controls	3.3±0.2	5.2±0.8			
LVPWT (mm)					
GHD	5.1±0.8	7.8±0.7	<0.05	<0.05	NS
Controls	7.5±0.2	6.9±0.2			
LVM (g)					
GHD	25.56±2.2	32.65±2.4	<0.05	<0.05	NS
Controls	31.43±3.1	31.54±2.2			
LVMI (g/m[2])					
GHD	47.0±6.9	71.5±12.7	<0.001	<0.001	NS
Controls	73.1±8.3	74.2±9.9			
E/A					
GHD	1.1±0.05	1.3±0.09	NS	NS	NS
Controls	1.2±0.04	1.2±0.06			
IRT (ms)					
GHD	52.11±14.9	50.0±10.0	NS	NS	NS
Controls	53.45±16.3	51.6±13.5			

NS: Not significant, *P*[1] GHD patients at baseline vs. controls, *P*[2] GHD patients at baseline vs. 1 yr of GH therapy, *P*[3] GHD patients after 1 yr of GH treatment vs. controls, GHD: Growth hormone deficiency, IRT: Isovolumetric relaxation time, LVMI: Left ventricular mass index, LVM: Left ventricular mass, LVPWT: Left ventricular posterior wall thickness, IVSWT: Interventricular septal wall thickness, FS: Fractional shortening, EF: Ejection fraction, LVESD: Left ventricular end-systolic diameter, LVEDD: LVEDD: Left ventricular end diastolic diameter, GH: Growth hormone

reported that LVM and systolic and diastolic functions did not differ from a control group after 1 year of GH therapy. The difference between our result and Radetti *et al*. results may be attributed to different GH dosages, duration of GH treatment, and degree of GHD severity. The difsferent degree of GHD may result in a different response to GH replacement, which might ultimately result in a varied increase in cardiac size.

In the present study, no abnormalities of LV systolic or diastolic function were identified in these GH-deficient children at baseline or after 1 year of rhGH therapy. Cardiac dysfunction and subsequent GH treatment amelioration may require a longer duration of GH deficiency.[16] The age of children included in the study ranged between 4 and 10 years, i.e. pre-pubertal, to rule out the possible influence of changes in insulin and other metabolic parameters as a result of pubertal development. In the present study, total, LDL cholesterol, AI, and insulin were significantly higher in children with GHD than in healthy controls at study entry. After 12 months of GH replacement therapy, total, LDL cholesterol, AI, and insulin were significantly decreased. This beneficial effect of GH treatment on lipid profile and AI has been reported in other short- and long-term studies evaluating the efficacy of GH therapy on lipid profile in GHD children.[20,21] In a 6-yr follow-up study, Van Der Sluis *et al*.[22] documented a long-term beneficial effect of GH therapy on AI, as well as on HDL cholesterol in GHD children. The same beneficial effect on lipid metabolism has been observed in children with short stature, born small for gestational age after 6 years of GH treatment.[23] It is well-known that abnormalities in lipid profile may severely increase the coronary risk of GHD patients;[24] thus, the decrease in the total/HDL cholesterol ratio during GH therapy can be clinically relevant to the prevention of CVD in midlife, because it represents one of the most efficient predictors of coronary heart disease in adults.[25] The exact mechanisms that underlie these changes are not fully understood, but GH may act through the regulation of both the activity of the cholesterol 17-alpha -hydroxylase enzyme and the regulation of LDL cholesterol receptor numbers.[26] On the other hand, Gleeson *et al*.[27] reported no beneficial effect of GH treatment on lipid profile. This difference may be explained by the variety of etiologies of GH deficiency, differences in severity and duration of this deficit, and the association with other pituitary hormone deficiencies. In the present study, no difference was seen between GH deficiency group and normal controls for HDL-C levels. This finding is in line with results of previous reports suggesting that normal HDLc is a feature of childhood onset GH deficiency as opposed to adult onset disease, which is associated with a reduced HDL-C.[28]

In the present study, insulin sensitivity was markedly affected, with a significant increase in HOMA-IR, related to increased levels of both insulin and fasting glycemia. Other studies have reported even increased insulin sensitivity in young pre- or early pubertal children, and that there is progressive deterioration in this insulin sensitivity with advancing age and pubertal development.[29,30]

Most short-term studies have reported a deterioration of insulin sensitivity, whereas long-term studies suggested that, after an initial worsening, insulin sensitivity returned toward baseline values.[31] Previous studies in short children have shown that short-term GH replacement was associated with development of insulin resistance and peripheral hyperinsulinemia, as measured by the hyperglycemic clamp technique or using oral glucose

tolerance testing, even if insulin levels remained within the physiological range of normal control children.[32,33] In short small-for-gestational-age children, GH replacement induces high fasting insulin levels with normal glucose. In addition, concern has been expressed that GH administration in children and adolescents may cause or exacerbate, in predisposed individuals, type 2 diabetes mellitus.[34] Growth hormone has antagonistic effects to that of insulin, and a decrease in insulin sensitivity has been reported in acromegaly, in puberty, or during growth hormone replacement therapy. Children with GHD have a larger tendency to present with hypoglycemia both fasting and induced, possibly due to an alteration in the regulation of counter regulatory hormones and an increase in insulin sensitivity. This susceptibility to hypoglycemia tends to diminish with age, and adults with GHD present with insulin resistance even before growth hormone administration; this could be due to changes in body composition, metabolic responses to growth hormone or to the interaction with sexual hormones. Growth hormone replacement therapy increases lypolysis with an increment in the concentrations of free fatty acids, which could diminish the uptake of glucose into skeletal muscle.[35] Studies using acipimox, a free fatty acid blocker, have confirmed the inverse relation that exists between circulating free fatty acid concentrations and insulin sensitivity in adults with GHD.[36] However, additional follow-up is necessary to evaluate whether insulin sensitivity will continue to worsen as an effect of GH therapy, or this mild increase may instead represent a component of the anabolic process of somatic development.

Conclusions

The results of the present study demonstrate that GHD in children is associated with a significantly reduced cardiac mass and impairment of lipid profile. GH replacement therapy exerts beneficial effects both on cardiac mass and lipid metabolism by normalizing cardiac size and reducing the AI. On the contrary, an increase in insulin resistance is observed after 1 year of GH treatment.

Recommendations

1. Children with GH deficiency should have echocardiography to observe the dynamics of the left ventricle functional disorders
2. Lipid profile monitoring is mandatory in children with GHD.

Limitations of the study

1. Small sample size
2. Possible confounders, including the potential effects of body mass index, change in the body composition (increased skeletal muscle), and physical activity
3. Echocardiography might not be sensitive enough to reveal minimal abnormalities in cardiac performance.

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