Growth Hormone Therapy Effects on Left Ventricular Function, Lipid Profile and Insulin Resistance

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Abstract:

Background: At present, there is a growing body of evidence implicating growth hormone (GH) and/or insulin-like growth factor-I (IGF-I) in the intricate cascade of events connected with the regulation of heart development and hypertrophy. In addition, advanced clinical manifestations of abnormal GH levels almost always include impaired cardiac function which may reduce life expectancy of those patients. Cardiac affection is probably related to a primary impairment of heart structure and function and to metabolic changes such as hyperlipidemia, increased body fat and premature atherosclerosis.

Aim: To evaluate the effect of growth hormone therapy on cardiovascular risk factors such as lipid profile, insulin resistance, and left ventricular systolic and diastolic function.

Patients and methods: This prospective cohort study was carried out at Pediatric Cardiology and Endocrinology Units of Children's Hospital and Clinical Pathology Laboratory, Faculty of Medicine, Zagazig University. Forty-one participants were included in the study. They were classified into growth hormone deficiency group: comprised 25 children and idiopathic short stature group comprised 16 children. Lipid profile and insulin resistance were assessed and Echocardiography was performed.

Results: There were statistically significant differences between studied groups regarding initial mitral A wave velocity (higher in GH deficiency) and E/A wave velocity ratio (higher in idiopathic short stature) while 6 months after therapy, both groups did not show significant difference. Within group of GH deficiency, there were significant increases in E wave velocity, E/A velocity ratio, E`/A` velocity ratio following rh-GH treatment. We found a significant negative correlation between percent of final height to lowest target height and age, initial Z score of BMI and initial SDS of height.

Conclusion: Using traditional Doppler, we found that LV early diastolic filling was better in GH deficient patients than in cases with idiopathic short stature and it was also better in terms of tissue Doppler-derived E`/A` velocity ratio in both groups of patients following rh-GH replacement. Among patients with GH deficiency, LV early diastolic function showed significant improvement after rh-GH treatment. After therapy with rh-GH at a median dose of 0.04 mg/kg/day, height, weight and SDS of height showed significant enhancement. The percentage of current height to the lowest target height correlated negatively with both initial Z score of BMI and SDS of initial height. Insulin resistance was higher in patients with GH deficiency compared to those with idiopathic short stature.

Keywords: Left ventricular function; Tissue Doppler;Lipid profile; Insulin resistance; Growth hormone.

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Introduction:

Growth hormone deficiency (GHD) has been recognized as a clinically relevant condition in children. Among the distinct features of the GHD, the cardiovascular involvement has convincingly emerged as particularly important. Studies in this field allowed a physiological role for GH in the regulation of heart function and structure to be elucidated or at least envisioned(1).

It is now established that children with 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, as well as reduced cardiac performance, all of which may contribute to a reduced life expectancy with increased morbidity and mortality for cardiovascular disease (CVD). The existing evidence indicates that atherosclerotic CVD begins in childhood (2).

In children with GHD, Echocardiographic studies of systolic function have yielded conflicting results on the effect of both GHD and GH therapy on cardiac performance. 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 patients at a higher risk of CVD at an early age (3).

Patient and methods

This prospective cohort study was carried out at Pediatric Cardiology and Endocrinology Units of Children's Hospital and Clinical Pathology Laboratory, Faculty of Medicine, Zagazig University from March 2022 to May 2023. Forty-one participants were included in this study. They were classified into 2 groups:

Group 1; Growth hormone deficiency group: comprised 25 children.

Group 2; Idiopathic short stature group: comprised 16 children.

Patients 4-10 years old, receiving growth hormone therapy for two years or more with normal thyroid function tests were included in this study.

Any acute severe illness during the previous 6 months, evidence of current cardiovascular disease, respiratory, renal, liver, or endocrine disease, children with dysmorphic phenotypes such as skeletal dysplasia or Turner syndrome, multiple pituitary hormone deficiencies, history of prematurity or intrauterine growth retardation, family history of atherosclerosis and/or cardiovascular disease, patients that are not welling to complete the study and patients receiving drugs that may affect blood glucose level were excluded from our study.

All patients were subjected to full history taking including cause of short stature : patients were subdivided into two groups based on results of stimulation of GH secretion by provocation tests ;clonidine test and results of serum insulin-like growth factor-1 at diagnosis of GH deficiency, thorough clinical examination including: body mass index (BMI) that was calculated as weight (kg) divided by square of the height (m^2), mid parent height that was calculated by taking the average of mother's and father's height after addition of 13 cm in boys or subtractions of 13 in girls while target height was calculated as before ±8 cm(4). All patients were investigated for CBC, liver function, kidney function tests (BUN, serum Creatinine), thyroid function (TSH , free T4), lipid profile (triglycerides, total cholesterol, LDL and HDL), insulin resistance (IR) that was calculated using the homeostasis model assessment method: HOMA-IR = fasting insulin (µU/ml) × fasting glucose (mmol/l)/22.5.(5)

Echocardiography

All patients underwent an Echocardiographic examination with simultaneous ECG tracing at baseline and 6 months thereafter. Patients were kept on GH replacement therapy in between the two Echocardiographic examinations. Echocardiography was performed in supine or left lateral decubitus with an Epiq CVx Release 6

Philips machine using S 8-3 and X5-1 MHz transducers. LV end-diastolic dimension and end-systolic dimension, interventricular septal end-diastolic dimension, and LV posterior wall end-diastolic dimension, and ejection fraction were measured by M- mode in the parasternal short-axis view (6).

LV mass (LVM) and LV mass indexing (LVMi) were performed by using LVMi calculator; The LVM was calculated by using Devereux's formula according to Penn's convention with the regression-corrected cube formula; LVM = 1.04 [(IVS+ LVEDD + PWT)^3 − (LVEDD)^3] −13.8 g. LVMi was obtained by correcting LVM for body surface area (7).

Diastolic mitral inflow velocity was measured in the apical four-chamber view with the conventional pulsed wave Doppler sample volume of 3 mm placed between the mitral leaflet tips; the early (E) and the late (A) diastolic mitral inflow velocity peaks were obtained followed by the calculation of the E/A ratio. Tissue Doppler sample volume of 3 mm was placed at the lateral annulus of mitral valve. Pulsed wave tissue Doppler was used to measure È (early diastolic) and À (late diastolic) wave peak velocities. È/ À velocity ratio was calculated. (8).

Tissue Doppler-derived isovolumic relaxation time (IVRT) was measured as the time interval between the end of aortic valve closure (end of S wave) and the onset of mitral valve opening (onset of È wave) (9).

Echocardiographic examinations were read and analyzed by a single observer blinded to patient history and laboratory test results.

Statistical Analysis

Data analysis was performed using the software SPSS (Statistical Package for the Social Sciences) version 26. The following tests were used: Chi square test, independent sample t-test, Pearson and Spearman rank correlation coefficients, paired sample t-test and Wilcoxon signed rank test. The level statistical significance was set at *P*<0.05. Highly significant difference was present if p≤0.001.

Results:

Table (1): Distribution of studied patients according to demographic data:

	N=41	%
Gender: Female Male	 24 17	 58.5% 41.5%
	Mean ± SD	Range
Age (year)	9.63 ± 0.66	8 – 10

This study included 41 patients 8 to 10 years old (mean age=9.63 years) and 58.5% of them were females (Table 1).

Table (2): Anthropometric measures among studied patients before and after therapy:

	At beginning of study	After six months of treatment	t	p
	Mean ± SD	Mean ± SD		
Height (cm)	133.42 ± 7.54	136.67 ± 7.28	-23.288	<0.001**
Weight (kg)	31.53 ± 7.94	33.01 ± 7.94	-16.706	<0.001**
BMI (kg/m^2)	17.45 ± 2.89	17.46 ± 2.81	-0.186	0.854
	Median (IQR)	Median (IQR)	Z	P
Z score of BMI	0.1(-0.5, 0.85)	0.2(-0.45, 0.85)	-0.861	0.389
SDS of height	-0.6(-1.2, 0.1)	-0.1(-0.6, 0.6)	-5.594	<0.001**

BMI: body mass index, IQR: interquartile range, t:Paired sample t test, Z: Wilcoxon signed rank test, **: p≤0.001 is statistically highly significant.

There was a statistically significant increase in height from 133.42 cm to 136.67 cm. There were statistically significant increments in height, weight, and SDS of height. On the other hand, there were non-significant rises in body mass index or its Z score (Table 2).

Table (3):Conventional and Tissue Doppler data among studied patients before and after therapy:

	At beginning of study	After six months treatment	t	P
	Mean ± SD	Mean ± SD		
E (cm/S)	90.18 ± 13.62	92.18 ± 18.34	-0.823	0.415
A wave (cm/S)	54.53 ± 14.5	52.66 ± 16.81	0.79	0.434
E/A	1.73 ± 0.45	1.86 ± 0.56	-1.558	0.127
E` (cm/S)	15.49 ± 2.91	16.34 ± 3.84	-1.736	0.09
A` (cm/S)	7.24 ± 2.4	6.3 ± 1.76	3.644	0.001**
E`/A`	2.28 ± 0.71	2.71 ± 0.83	-4.29	<0.001**
IVRT (mS)	65.66 ± 12.71	63.18 ± 12.54	1.242	0.222

A: late diastolic mitral inflow peak velocity, A`: late diastolic mitral peak tissue velocity, E: early diastolic mitral inflow peak velocity, E`: early diastolic mitral peak tissue velocity,IVRT: isovolumic relaxation time, t: Paired sample t test, **: p≤0.001 is statistically highly significant.

There was a statistically significant decrease in A` (from 7.24 cm/s to 6.3 cm/s) while there was a significant rise in E`/A` (from 2.28 to 2.71). There were statistically non-significant increases in E, E/A, or E`. we reported non-significant reductions in A wave and IVRT 6 months after therapy (Table 3).

Table (4):Comparison between the studied groups regarding tissue Doppler data before and after therapy

	Idiopathic	GH deficiency	t	P
	Mean ± SD	Mean ± SD		
E (cm/S)				
Initial	91.76 ± 11.93	89.17 ± 14.74	0.588	0.56
6 months	85.01 ± 15.82	96.77 ± 18.66	-2.084	0.044*
p¥	0.034*	0.021*		
A wave (cm/S)				
Initial	47.92 ± 11.29	58.77 ± 14.92	-2.484	0.017*
6 months	50.44 ± 17.35	54.08 ± 17.35	-0.67	0.507
p¥	0.581	0.079		
E/A				
Initial	1.95 ± 0.37	1.59 ± 0.45	2.695	0.01*
6 months	1.79 ± 0.47	1.9 ± 0.61	-0.574	0.569
p¥	0.165	0.004*		
E` (cm/S)				
Initial	15.21 ± 3.06	15.66 ± 2.86	-0.48	0.634
6 months	16.32 ± 4.27	16.32 ± 3.63	0.034	0.973
p¥	0.21	0.272		
A` (cm/S)				
Initial	6.34 ± 2.02	7.81 ± 2.48	1.983	0.054
6 months	6.11 ± 1.48	6.43 ± 1.94	-0.575	0.568
p¥	0.449	0.001**		

E`/A` Initial 6 months	 2.52 ± 0.85 2.78 ± 0.94	 2.13 ± 0.57 2.67 ± 0.76	 1.722 0.392	 0.084 0.697
p¥	0.035*	<0.001**		
IVRT (ms) Initial 6 months	 66.69 ± 8.58 61.31 ± 14.22	 65.0 ± 14.9 64.37 ± 11.5	 0.41 -0.758	 0.684 0.453
p¥	0.083	0.817		

A: late diastolic mitral inflow peak velocity, A`: late diastolic mitral peak tissue velocity, E: early diastolic mitral inflow peak velocity, E`: early diastolic mitral peak tissue velocity, IVRT: isovolumic relaxation time,t: independent sample t-test,p¥: p for paired sample t-test, *p<0.05 is statistically significant, **p≤0.001 is statistically highly significant.

There were statistically significant differences between studied groups regarding initial A wave velocity (higher in GH deficiency) and E/A wave velocity ratio (higher in idiopathic short stature). There was a statistically significant variation between studied groups regarding E wave velocity six months after therapy (higher in GH deficiency) but the difference was non-significant concerning baseline E wave velocity. There were statistically non-significant differences between studied groups regarding IVRT, E`wave velocity, A` wave velocity or E`/A` velocity ratio initially or 6 months after therapy. Within the GH deficiency group, there were significant increments in E velocity, E/A velocity ratio, E`/A` velocity ratio and a significant drop in A`wave velocitywith non-significant changes in E` or A wave velocities. Within the group of idiopathic short stature, there was a significant decrease in E wave velocity, and a significant increase in E`/A` velocity ratio with non-significant changes in A wave velocity, E/A velocity ratio, E` or A`wave velocities (Table 4).

Table (5):Correlation between dose, duration of therapy and biochemical profile:

	Dose		Duration	
	R	P	r	P
HOMA-IR	0.241	0.128	0.137	0.394
FBG	0.247	0.13	-0.099	0.549
Fasting insulin	0.244	0.124	0.169	0.209
Atherogenic index	-0.003	0.995	0.164	0.305
HDL cholesterol	0.032	0.841	0.113	0.482
LDL cholesterol	-0.045	0.778	0.102	0.526
Total cholesterol	-0.07	0.666	0.158	0.323
Triglycerides	-0.021	0.896	-0.036	0.823

HOMA-IR:homeostasis model assessment method for insulin resistance calculation, r: Spearman rank correlation coefficient.

We reported non-significant correlation between dose or duration of GH treatment and any of the studied biochemical parameters (Table 5).

Table (6):Correlation between dose, duration of therapy and Doppler data:

	Dose		Duration	
	R	p	R	P
E (cm/S)	0.286	0.07	0.027	0.869

A wave (cm/S)	0.165	0.303	0.073	0.65
E/A	-0.044	0.785	-0.044	0.783
E` (cm/S)	0.101	0.531	0.128	0.425
A` (cm/S)	-0.145	0.366	0.153	0.338
E`/A`	0.212	0.184	-0.088	0.586
IVRT	-0.143	0.372	0.208	0.191

A: late diastolic mitral inflow peak velocity, A`: late diastolic mitral peak tissue velocity, E: early diastolic mitral inflow peak velocity, E`: early diastolic mitral peak tissue velocity, IVRT: isovolumic relaxation time, r: Spearman rank correlation coefficient.

There were non-significant correlations between dose of GH therapy and either Ewave velocity, A wave velocity, E/A blood velocity ratio, E`wave velocity, A`wave velocity, E`/A` tissue velocity ratio or IVRT. There were non-significant correlation between duration of GH replacement and either Ewave velocity, A wave velocity, E/Ablood velocity ratio, E`wave velocity, A`wave velocity, E`/A` tissue velocity ratioor IVRT (Table 6).

Table (7):Correlation between percent of current height to lowest target height and baseline data:

	Percent of current height to lowest target height	
	R	P
Age (years)	-0.458	0.003*
SBP (mmHg)	-0.212	0.182
DBP (mmHg)	-0.297	0.06
Heart rate (b/min)	0.134	0.405
Oxygen saturation (%)	0.097	0.545
Hemoglobin (g/dl)	-0.108	0.501
TSH (µiu/ml)	-0.079	0.626
Free T3 (ng/dl)	0.08	0.62
Cholesterol (mg/dl)	-0.19	0.233
HDL cholesterol(mg/dl)	-0.155	0.332
FBG (mg/dl)	0.155	0.347
HOMA-IR	-0.2	0.21
Atherogenic index	-0.089	0.582
Fasting insulin	-0.229	0.15
Z score of initial BMI	-0.478	<0.001**
SDS of initial height	-0.504	<0.001**

FBG: fasting blood glucose, HOMA-IR: homeostasis model assessment method for insulin resistance calculation,r: Pearson correlation coefficient, *p<.05 is statistically significant.

We found significant negative correlation between percent final height from lowest target height and age, initial Z score of BMI and initial SDS of height with non-significant correlation regarding other baseline parameters (Table 7).

Table (8): Correlation between percent of final height from lowest target height and Doppler data.

	Percent of final height from target height	
	R	P
E (cm/S)	0.117	0.467
A wave (cm/S)	-0.059	0.714
E/A	0.079	0.624

E` (cm/S)	-0.09	0.576
A` (cm/S)	-0.274	0.083
E`/A`	0.115	0.473
IVRT	0.306	0.052

A: late diastolic mitral inflow peak velocity, A`: late diastolic mitral peak tissue velocity, E: early diastolic mitral inflow peak velocity, E`: early diastolic mitral peak tissue velocity, IVRT: isovolumic relaxation time, r: Pearson correlation coefficient, *p<0.50 is statistically significant.

There is non-significant negative correlation between percent final height from target height and Doppler Echocardiographic parameters (Table 8).

Discussion:

Growth hormone deficiency (GHD) has been recognized as a clinically relevant condition in pediatric patients. Among the distinct features of the GHD, cardiovascular involvement has convincingly emerged as particularly vital. Studies in this field allowed a physiological role for GH in the regulation of cardiac function and structure to be clarified(1, 10).

It is now established that children with GHD may develop a group of cardiovascular risk factors, including uncomplimentary lipid profile, increased body fat, premature atherosclerosis, diminished fibrinolytic activity, augmented peripheral insulin resistance, as well as reduced cardiac performance, all of which may contribute to a reduced life expectancy with an increased mortality for cardiovascular disease (CVD). The current evidence indicates that atherosclerotic CVD begins in childhood (2).

In children with GHD, Echocardiographic studies of systolic function have yielded conflicting results on the effect of both GHD and GH therapy on cardiac performance (4). On the other hand, relatively fewer studies have investigated the effect of GHD and GH replacement therapy on cardiac performance and metabolic abnormalities that may place patients at a higher risk of CVD at an early age (3, 11).

We aimed to evaluate the effect of growth hormone therapy on cardiovascular risk factors as lipid profile, insulin resistance, and left ventricular diastolic and systolic function.

This prospective cohort study included 41 participants aged 4-10 years, The study was performed at Cardiologyand Endocrinology Units at Pediatric Department, Zagazig university hospitals.

Sędek et al. studied 117 children treated with GH for 1-4 years. They reported a mean height SDS of –2.6 ±0.56 and a mean weight SDS of –0.3 (–0.7-0.2) (12).

Smyczynska et al. investigated 75 children (59 boys, 16 girls) with disorders of GH secretion and stated that the mean height SDS was -2.59 ± 0.53 (13). In our study both height and weight increased significantly after growth hormone therapy (table 2).

Experience gained during the last 15–20 years has shown that GH treatment is effective in restoring normal growth in children with GHD and other forms of growth retardation, including idiopathic short stature (ISS) and small for gestational age (SGA) with insufficient catch-up growth. Meta-analysis of results from 21 clinical studies indicated that children with ISS who received rh-GH had significantly higher height increment at the end of the first year than the control group, an effect that persisted in the second year of treatment. This treatment also improved final adult height. The difference between the 2 groups was equal to 5.3 cm for male patients and 4.7 cm for female patients (14). Results of a large observational study in Korea demonstrated increased height standard deviation score (SDS) from the baseline in subjects with GHD and ISS (15).

Chen et al. performed a prospective case–control study. In total, 60 cases of isolated GHD children aged 5–10 years were divided into two groups; group A received rh-GH 0.23 mg/kg/week and group B received rh-GH 0.35

mg/kg/week and found that the mean height was 114.62 ± 9.37 cm before treatment and was 125.04 ± 9.37 cm after treatment. (16).

In our present study, there was a statistically significant elevation in height from 133.42 cm to 136.67 cm. There was a statistically significant increase in weightand SDS of height. On the other hand, there was a non-significant change in body mass index or in its Z score (table 2).

Ozdemir et al. studied twelve children (6 male and 6 female patients) with GHD (mean age of 11.04 ± 3.09 years). The mean height and BMI of were 125.5 ± 15.4 cm and 17.9 ± 4.22kg/m^2, respectively. All patients had isolated GHD and had received rh-GH for a period of 5.86 ± 1.61 months. Recombinant human growth hormone was administered subcutaneously 7 times/week at a dose 25 mg/kg/day. The injection site was either over the abdomen or the anterior thigh according to patient's preference. After rh-GH treatment, mean height and BMI of patients were to 131.6 ± 17.9 cm and 17.8 ± 3.84kg/m^2respectively (7).

Gómez-Guzmán et al. studied left ventricular mass and function in children with growth hormone deficiency after replacement treatment on 81 children. They compared 40 GHD children (16 males and 24 females) to 41 healthy children (control group) and reported that weight, height, and body surface area were significantly lower, as expected, in GHD children than in controls. After 6 months of GH replacement therapy, weight (30.36 ± 7.81 kg), height (131.88 ± 10.9 cm), and body surface area (1.05 ± 0.17 m^2) were measured and compared to the same groups values before treatment had been started, and there were differencescoinciding with our findings (p values = 0.000) . (17).

McCaughey et al. have reported the results of a randomized study in ten girls aged 6.2±0.4 years with short stature treated for a mean period of 6.2 years at a dose of 0.06 mg/kg daily. Mean final height was 7 cm greater than that observed in the control group, and all treated girls reached their genetic target, whereas only 38% of the untreated girls reached the genetic target (18). Leshek et al. reported that mean final height in 22 children with ISS 12.5±1.6 years old treated at a dose of 0.22 mg/kg per week (divided in three injections per week) for 4.4±1.6 years was 0.5 SDS greater than the control group (19). In the study conducted byAlbertsson-Wikland et al., the mean final height of 49 children 11.5±1.3 yearsold with ISS treated by GH at a dose of 0.033-0.067 mg/kg daily was 0.6 SDS greater than in the control group (20). A large individual variability of response was observed in those studies. A number of factors have been indicated as predictive of the final outcome, including age and height at start of treatment; the younger and taller the better, first year response, dose of GH, and mid parental height (21).

However, Sędek et al. showed that after the initiation of rh-GH therapy, significant reduction in height deficit resulting from an increase in height velocity coinciding with an increase in IGF-1 SDS values. They concurrently found that fT4 levels were significantly decreased compared to baseline. This may be due to relatively small sample size (12).

In the present study, we showed a significant increase in E`/A` velocity ratio from 2.28 to 2.71 which denotes some improvement in LV early diastolic function after rh-GH replacement. There were statistically non-significant elevations in E wave velocity, E/A blood velocity ratio, or E` wave velocity while there were non-significant decrements in A wave velocity and IVRT 6 months after therapy (table 3).

By M-mode Echocardiography, Ozedemir et al. showed that there were no significant changes (P>0.05) in thicknesses of the posterior wall and interventricular septum, aorta and left atrial diameters, or LV shortening fraction all over the study period. Left ventricular internal systolic dimensions were significantly larger with rh-GH therapy (21.4±2.63 to 24.0± 4.13 mm; P = 0.03) and diastolic dimensions also increased (36.5 ± 3.90 to 39.5 ± 4.94 mm; P<0.01). Regarding the conventional Doppler Echocardiography, there were statistically significant differences in parameters, such as deceleration time of early

peak velocity of mitral valve inflow, IVRT, and myocardial performance index (P<0.01). However, mitral and tricuspid E/A wave velocity ratios did not differ during rh-GH therapy (P>0.05) (7).

Gómez-Guzmán et al.showed that the systolic and diastolic diameters of LV were significantly lower in GHD children than in controls, although within normal values for age.After 6 months of treatment the systolic diameter of the LV was not modified while its diastolic diameter increased. After 6 months with recombinant GH, values of diastolic LV diameter were similar to the controls (p = 0.208).EF, E/A velocity ratio, E/E' velocity ratio, and IVRT were similar in GHD children to those in controls. After treatment, Gómez-Guzmán et al. compared GH group to the control group and found that EF and IVRT experienced slightly significant reductions(17).

Using conventional Doppler examination, we found that there were statistically significant differences between studied groups regarding initial mitral A wave velocity (higher in GH deficiency) and E/A wave velocity ratio (higher in idiopathic short stature) while 6 months after therapy, both groups did not show significant difference.These findings suggest presence of late diastolic dysfunction in GH deficiency group with normalization of diastolic function after 6 months of rh-GH replacement. There were statistically non-significant differences between studied groups regarding IVRT, E`wave velocity, A` wave velocity or E`/A` velocity ratio whether initially or 6 months after therapy. Within group of GH deficiency, there were significant increases in Ewave velocity, E/Avelocity ratio, E`/A` velocity ratio following rh-GH treatment. On the other hand, there were non-significant changes in E` or A wave velocities.The increase in E wave velocity and consequently E/A velocity ratio in our patients with GH deficiency reflects an improvement of early diastolic filling of LV after 6 months of rh-GH replacement (table 4).

Heterogeneous GH effects have also been reported on systolic functional indices as cardiac output, fractional shortening (FS) and ejection fraction (EF). The increase in cardiac output seen in some trials is probably related to the small upsurges in heart rate and stroke volume. Stroke volume was the only parameter to be significantly augmented in subgroup analysis of some randomized trials, although the small number of trials together withlimited study populations restrict the reliability of this conclusion. The capacity of GH to increase contractility is controversial. Some studies have shown an increase in fractional shortening, whereas others showed no variation(22).

Maison et al. in their meta-analysis showed a trend toward a positive effect of GH on fractional shortening(23). In fact, a study demonstrated that GH treatment was able to modify vascular reactivity in improving endothelium-dependent and endothelium non-dependent vasodilatation, which were impaired in patients with GHD as compared with normal control subjects (24).

Retrospective studies observed no change in left ventricular function or morphology during 2 years of rh-GH treatment in children without pre-existing cardiac disease (25). The findings reported by Barton et al. (26) differ from those reported in some GHD patients treated with rh-GH in whom an increase in left ventricular wall thickness and LVMI has been reported (26, 27). In some studies, myocardial atrophy is postulated to result from long-standing GHD and normalization of these parameters follows hormone replacement (27); in others, initially normal cardiac indices have shown a modest increase but remained within the normal range (28). The mildrise in LVMI observed after 2 years treatment with high dose rh-GH falls within the 95% confidence interval for the estimation of mean LV mass (29).In patients receiving 40IU/ m^2/week rh-GH, indexed LV mass was significantly higher than baseline values after 2 years of treatment (P = 0.04) but still remained within the normal range (30)

Barton et al. showed that FS did not differ from controls after 12 months rh-GH treatment and remained within the normal range (28-44%) after 2 years of therapy; median (range) for FS

were 35 (29-42)% (observation group), 36.5 (25-42)% (20 IU/m^2/week group) and 36.5 (25-43) % (40 IU/ m^2/week group) at one year (P = 0.94); and were 38 (31-42)% and 35 (29-46)% respectively in the standard and high dose rh-GH groups after 2 years of treatment. No significant increase in FS from baseline was observed with either rh-GH dose at 1 or 2 years of treatment(26).

In our study there was non-significant correlation between dose or duration of GHand HOMA-IR, fasting blood glucose, fasting insulin, lipid profile (table 5).Similarly,Kim et al. showed that there were no significant correlations between GH interruption period and lipid profile or anthropometric parameters (31).

Previous studies raised concerns over increased insulin resistance and impaired fasting glucose during GH treatment, especially in patients with obesity. Studies in children and adolescents also suggested that GH administration may induce insulin resistance after short-term treatment, but its long-term consequences have not been fully determined yet. Several cohort studies indicate that GH therapy may increase the incidence of type 2 diabetes mellitus in children and adolescents with predisposing risk factors, therefore it is prudent to monitor possible negative consequences on glucose metabolism during and after GH administration (32).

We found non-significant correlation between dose of GH and any of the studied conventional and tissue Doppler trans-mitral parameters including E wave velocity, A wave velocity, E/A blood velocity ratio, E` wave velocity, A` wave velocity, E`/A` tissue velocity ratio or IVRT. Similarly, there was non-significant correlation between duration of therapy and any of the aforementioned parameters (table 6).

Gómez-Guzmán et al. showed that after rh-GH replacement therapy, cardiac size and LV mass increased, with no negative effects on diastolic function. There were studies establishing similar changes to those observed but over a shorter time period of 6 months only. Treatment with this hormone seems to have short-term effects, which have not been previously described. Such effects most likely coincide with the period of greater increase in growth rate (17).Minczykowski et al. assessed the cardiac dimensions and function before and after 12 months of GH treatment in patients with GH deficiency. The study has shown that GHD patients have cardiac dysfunction, as evidenced by a depressed ejection fraction (eight patients with an EF < 55%). Treatment with GH for 12 months increased the ejection fraction in association with a decrease in left ventricular end-systolic volume but without any significant change in end-diastolic volume (33).

Other studies did no observe any benefit at the dose of 0.17–0.67 mg/day for 26 weeks of rh-GH (34). However, Napoli et al. observed improvement of the endothelial function in 16 patients treated with 1.33 mg of GH every second day after a period of three months, highlighting the potential role of GH in delaying the progression of HF (35). The conflicting results of the clinical trials with GH therapy in HF may be related to the small number of patients enrolled, the different dose and duration of GH treatment, the heterogeneity of cardiac heart failure etiologies, and differences in the patients' clinical characteristics (36).

In this study, there was significant negative correlation between percent final height from lowest target height and age, initial Z score of BMI and initial height SDS. On the contrary, we found non-significant correlation concerning other baseline clinical and biochemical parameters (table 7).

Abdou et al. elucidated that patient's height was negatively correlated to the age at which GH medication was commenced (r= - 0.525, P= 0.003); the older the patients at the onset of GH therapy, the shorter they were during the course of this research (37). Similarly, other studies investigating the influence of age at growth hormone therapy initiation on near adult height in children with isolated GH insufficiency concluded that early GH administration increased the likelihood of reaching genetic height potential (38) .

Grimberg et al. observed that variables correlated with total height increment (ΔHt SDS) on multivariate analysis comprised mid-parental target height, height gain in the first year, height at the start of GH treatment, and duration of GH treatment. Baseline variables that predicted favorable height outcome included younger age at start of GH treatment, greater bone age delay, prepubertal status, and severe GHD. In their cohort, 65% were prepubertal at baseline and 48% had peak GH secretion between 7 and 10 µg/L, raising concern that a significant proportion of patients had constitutional delay of growth and puberty (39).

Van Pareren et al. clarified that an average of 7.8 years of continuous treatment with GH resulted in normalization of height during childhood and normalization of adult height (above -2 SDS) in 85% of the patients(40).

In our study, we detected non-significant correlation between percent final height from target height and the measured conventional and tissue Doppler parameters (table 8).

Conclusion:

Using traditional Doppler, we found that LV early diastolic filling was better in GH deficient patients than in cases with idiopathic short stature and it was also better in terms of tissue Doppler-derived E`/A` velocity ratio in both groups of patients following rh-GH replacement. Among patients with GH deficiency, LV early diastolic function showed significant improvement after rh-GH treatment. After therapy with rh-GH at a median dose of 0.04 mg/kg/day, height, weight and SDS of height showed significant enhancement. The percentage of current height to the lowest target height correlated negatively with both initial Z score of BMI and SDSof initial height. Insulin resistance was higher in patients with GH deficiency compared to those with idiopathic short stature. Our findings highlight the importance of periodic evaluation of LV function and Glucose metabolic abnormalities in patients receiving rh-GH. Larger scale and longer term follow up studies are needed to confirm our verdicts.

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