The Egyptian Journal of Hospital Medicine (July 2023) Vol. 92, Page 6062- 6069

Left Ventricular Mass after Growth Hormone Replacement Therapy

Ihab A Ahmed[1], *Ahmed AlAmir[1], Hanan S Ahmed[2], Heba Abouzeid[1]
Pediatrics Department [1], Clinical Pathology Department [2], Zagazig University, Egypt
***Corresponding author:** Ahmed AlAmir, **Email:** ahmedelamir106@gmail.com, **Mobile:** 01014662848

ABSTRACT

Background: Adults with growth hormone deficiency (GHD) have a number of cardiovascular risk factors that may enhance their risk of cardiovascular morbidity and mortality. The impact of growth hormone (GH) therapy on heart function and metabolic abnormalities that may increase children's risk of cardiovascular disease (CVD) at an early age has been the subject of very few research in children.

Aim: To evaluate the effect of growth hormone therapy on left ventricular mass. **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. In total, 41 people took part while studying. Two groups were created out of them: those with idiopathic short stature, which included 16 children, and those with growth hormone insufficiency, which included 25 children. To determine LV mass, Echocardiography was used.

Results: The left ventricular mass increased in a statistically meaningful way (from 83.4 g to 89.57 g) after GH therapy.

Conclusion: LV mass increased remarkably in our patients after GH therapy .LV mass correlated positively with duration of GH therapy and negatively with the percentage of final height to lowest target height.

Keywords: Left ventricular mass; Growth hormone.

INTRODUCTION

Growth hormone (GH) is crucial for somatic development and metabolic control. As it enhances glucose uptake, utilization, and inhibits gluconeogenesis, insulin lowers postprandial blood sugar and glycogenolysis [(1)].

GH is considered as a determinant of heart growth. Left ventricular (LV) hypertrophy and cardiac dysfunction are linked to GH overproduction [(2)].

Impaired cardiac functioning have been linked to growth hormone insufficiency as one of the main causes. Cardiovascular dysfunction is characterized by a decline in LV mass, a reduced ejection fraction, and abnormalities in LV diastolic filling. Recombinant human growth hormone therapy may improve contractility, increase exercise capacity, and raise LVEF in some GHD patients. mass, and increase cardiac output. Additionally, excessive growth hormone is linked to heart dysfunction and LV enlargement [(3)].

A beneficial non-invasive imaging technique frequently utilized in a variety of pediatric heart conditions is Echocardiography. It has been suggested that tissue doppler imaging (TDI) is useful for assessing early alterations in systolic and diastolic cardiac dysfunction. Age, heart rate, and preload have less of an impact on the TDI results than they do on traditional Echocardiography. These variables have been linked to cardiovascular disease-related mortality and morbidity in the past. Therefore, it may be concluded that TDI is a valuable method for identifying subclinical myocardial disease [(4)].

Aim: Evaluating growth hormone treatment's effects on the bulk and systolic function of the left ventricle.

Objectives:

- To asses left ventricular mass (LVM) and left ventricular mass index (LVMi) in children receiving growth hormone.
- To asses LV systolic function in children receiving growth hormone therapy using Echocardiography.

PATIENT AND METHODS

From March 2022 to May 2023, this prospective cohort study was conducted at the Children's Hospital Pediatric Cardiology and Endocrinology Units and Clinical Pathology Department. In this study, 41 children were enrolled. They were split into two categories: Group 1; that included growth hormone deficiency group: comprised 25 children and Group 2 that included Idiopathic short stature group which comprised 16 children.

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

Children with dysmorphic traits such as Turner syndrome or skeletal dysplasia with evidence of present cardiovascular disease, respiratory, renal, hepatic, or endocrine disease, multiple pituitary hormone deficiency, history of prematurity or intrauterine growth retardation, family history of cardiovascular disease or atherosclerosis, patients that are not welling to complete the study and patients receiving drugs that may affect blood glucose level were excluded from the study.

Body mass index (BMI), which is calculated as weight (kg) divided by square of height (m), and mid parent height (taki) that was calculated by taking the average of mother's and father's height after addition of 13 cm in

Received: 08/02/2023
Accepted: 10/04/2023

boys or subtractions of 13 in girls while target height was calculated as before ±8 cm [5].

Echocardiography

At baseline and again six months later, all patients underwent an echocardiogram while an ECG was also being recorded. Patients continued receiving GH replacement treatment in between the two echocardiographic examinations. Using a Philips Epiq CVx Release, Echocardiography was carried out when the patient was supine or lying on their left side 6 device with S 8-3 and X5-1 MHz transducers. In the parasternal short-axis view, M-mode was used to measure the diameters of the main and branch pulmonary arteries, the left atrium, the aorta, the left ventricle's (LV) end-diastolic dimension and end-systolic dimension, the interventricular septum, the left ventricle's posterior wall, and fractional shortening [6].

With the LVMi calculator, LV mass (LVM) and LV mass indexing (LVMi) were conducted; Using the regression-corrected cube formula and Devereux's formula in accordance with Penn's convention, the LVM was obtained; LVM = 1.04 $[(IVS+ LVEDD + PWT)^3 - (LVEDD)^3] -13.8$ g. LVMi was done by correcting LVM for body surface area [3]. Regional Increased LV mass can be classified as concentric hypertrophy or eccentric hypertrophy depending on the thickness of the wall (RWT) equals or exceeds 0.42. Regional wall thickness was obtained via online RWT calculator.

A single observer who was unaware of the patient's medical background and results of any laboratory tests examined and assessed echocardiographic examinations.

Ethical Approval:

All participants in the study provided their informed permission. Approval from Institutional review board (IRB), Faculty of Medicine, Zagazig University was obtained. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical Analysis

Data analysis was done using SPSS (Statistical Package for the Social Sciences) version 26. Depending on the type of data, the mean SD or median (range) was employed. The tests used were as follows: the spearman rank correlation coefficient, the paired sample t-test, and the independent sample t-test. P 0.05 was used as the statistical significance level. There was a quite substantial difference if $p \leq 0.001$.

RESULTS

41 Patients in this study ranged in age from 8 to 10 years old (mean age=9.63±0.66 years) and 58.5% (24 patients) of them were females.

Initial height of patients ranged from 108.5 to 145 cm with a mean of 133.42 ± 7.54 cm while mid-parent height with a mean of 166.12 9.67 cm and a range of 155 to 180 cm. Target height was 150 to 180.7 cm, with a mean height of 164.02 ± 12.81 cm. After therapy, percent of current attainable height to lowest targeted height ranged from 1.01% to 32.93% with a median of 11.33%. Percent of current of height to mid parent height ranged from 6.09 to 36% with a median of 15.74%

Table (1): M mode Echocardiographic data among studied patients before and after therapy:

	Before treatment	After treatment	t	P
	Mean ± SD	Mean ± SD		
LV mass (g)	83.4 ± 32.18	89.57 ± 33.99	-2.798	0.008*
LVMI (g/m^2)	76.61 ± 25.82	79.62 ± 25.82	-1.585	0.121
FS (%)	37.24 ± 5.66	36.31 ± 4.53	1.095	0.28
PA (mm)	18.89 ± 3.27	19.99 ± 3.71	-2.387	**0.022***
RPA (mm)	9.9 ± 2.45	10.31 ±2.75	-1.493	0.143
LPA (mm)	8.86 ± 1.91	9.32 ± 1.72	-1.671	0.102
AORTA (mm)	23.25 ± 3.56	23.93 ± 3.0	-2.127	**0.04***
LA (mm)	25.59 ± 4.27	25.84 ± 3.6	-0.514	0.61
IVS (mm)	7.05 ± 1.51	6.97 ± 1.25	0.475	0.637
LVPW (mm)	6.55 ± 1.23	6.79 ± 1.22	-1.455	0.154
LVIDD (mm)	41.38 ± 6.66	42.89 ± 5.73	-3.135	**0.003***
LVIDs (mm)	26.03 ± 4.85	27.86 ± 4.84	-2.769	**0.008***
RWT (mm)	0.32 ± 0.07	0.32 ± 0.05	0.548	0.578

EF: ejection fraction, FS: fractional shortening, , IVS: inter-ventricular septum, , LA: left atrium, LPA: left pulmonary artery, LVIDD: left ventricular internal diameter end diastole, LVIDS: left ventricular internal diameter end systole, LVMI: left ventricular mass index, LVPW: left ventricular posterior wall, **p≤0.001 is statistically highly significant, PA: main pulmonary artery, RPA: right pulmonary artery, RWT : regional wall thickness, t: Paired sample t-test.

There was a statistically significant increase in left ventricular mass (from 83.4 ± 32.18 to 89.57 ± 33.99 g) while there were significant increments in PA (from 18.89 ± 3.27 to 19.99 ± 3.71 mm), Aorta (from 23.25 ± 3.56 to 23.93 ± 3.0 mm), LVIDD (from 41.38 ± 6.66 to 42.89 ± 5.73) and LVIDs (from 26.03 ± 4.85 to 27.86 ± 4.84 mm). There was a statistically non-significant change in LVMI, fraction shortening, RPA, LPA, LA, IVS, LVPW or RWT (Table 1).

Table (2): Comparison between the studied groups regarding M mode echocardiographic data before and after therapy

		Idiopathic	GH deficiency	T	P
		Mean ± SD	Mean ± SD		
LV mass (g)	Initial	75.64 ± 32.47	88.37 ± 31.64	-1.224	0.221
	6 months	83.37 ± 31.64	93.67 ± 33.59	-0.967	0.34
	p¥	0.109	**0.032***		
LVMI (g/m²)	Initial	69.85 ± 29.54	80.93 ± 22.71	-1.355	0.183
	6 months	74.66 ± 28.55	82.79 ± 23.97	-0.983	0.332
	p¥	0.215	0.373		
FS (%)	Initial	39.17 ± 6.03	36.01 ± 5.15	1.791	0.081
	6 months	38.01 ± 3.69	35.22 ± 3.75	1.991	0.054
	p¥	0.394	0.493		
PA (mm)	Initial	18.61 ± 3.75	19.06 ± 2.99	-0.432	0.668
	6 months	20.04 ± 3.84	19.96 ± 3.71	0.073	0.942
	p¥	0.164	0.054		
RPA (mm)	Initial	9.73 ± 2.96	10.01 ± 2.12	-0.349	0.729
	6 months	10.32 ± 3.24	10.31 ± 2.45	0.012	0.99
	p¥	0.155	0.439		
LPA (mm)	Initial	8.53 ± 2.17	9.08 ± 1.73	-0.9	0.374
	6 months	9.01 ± 2.11	9.52 ± 1.43	-0.92	0.363
	p¥	0.319	0.209		
AORTA (mm)	Initial	22.62 ± 3.55	23.65 ± 3.58	-0.901	0.373
	6 months	23.35 ± 3.12	24.3 ± 3.12	-0.988	0.329
	p¥	0.211	0.112		
LA (mm)	Initial	25.1 ± 4.44	25.9 ± 4.22	-0.576	0.568
	6 months	25.07 ± 2.73	26.34 ± 4.04	-1.101	0.277
	p¥	0.959	0.518		
IVS (mm)	Initial	6.71 ± 1.85	.26 ± 1.23	-1.14	0.261
	6 months	6.66 ± 1.3	7.16 ± 1.2	-1.255	0.217
	p¥	0.886	0.579		
LVPW (mm)	Initial	6.23 ± 1.34	6.76 ± 1.14	-1.344	0.187
	6 months	6.61 ± 1.51	6.9 ± 1.02	-0.719	0.476
	p¥	0.126	0.528		
LVIDD (mm)	Initial	40.29 ± 6.64	42.08 ± 6.71	-0.839	0.406
	6 months	42.06 ± 4.83	43.42 ± 6.28	-0.737	0.466
	p¥	0.093	**0.011***		
LVIDs (mm)	Initial	24.29 ± 5.29	27.15 ± 4.28	-1.905	0.064
	6 months	27.09 ± 6.04	28.35 ± 3.95	-0.809	0.424
	p¥	0.091	**0.01***		
RWT (mm)	Initial	0.32 ± 0.08	0.32 ± 0.07	-0.383	0.703
	6 months	0.31 ± 0.06	0.32 ± 0.05	-0.478	0.635
	p¥	0.723	0.684		

FS: fractional shortening, , IVS: inter-ventricular septum, , LA: left atrium diameter, LPA: left pulmonary artery diameter, LVIDD: left ventricular internal diameter end diastole, LVIDS: left ventricular internal diameter end systole, LVMI: left ventricular mass index, LVPW: left ventricular posterior wall, p¥: p For paired sample t-test, *p<0.05 is statistically significant, **p≤0.001 is statistically highly significant, PA: main pulmonary artery diameter , RPA: right pulmonary artery diameter, RWT : regional wall thickness, , t: independent sample t-test.

There were statistically non-significant changes between studied groups regarding LV mass, LVMI, LA, PA, RPA, LPA, aorta, LVPW, LVIDD, LVIDS, or FS.

Within group of GH deficiency, there were significant increments in left ventricular mass, LVIDD and LVIDs after therapy while there were non-significant changes in other parameters. Within group with idiopathic short stature, there is non-significant change in M mode echo data (Table 2).

Table (3): Correlation between dose, duration of GH therapy and M Mode echocardiographic data:

	Dose		Duration	
	R	P	R	P
LV mass (g)	0.042	0.794	0.389	**0.012***
LVMI (g/m^2)	0.072	0.654	0.201	0.207
FS (%)	-0.298	0.058	0.19	0.234
PA (mm)	-0.031	0.847	0.076	0.636
RPA (mm)	-0.167	0.296	-0.033	0.836
LPA (mm)	-0.036	0.823	0.166	0.3
AORTA (mm)	0.023	0.888	0.24	0.131
LA (mm)	0.093	0.562	0.129	0.421
IVS (mm)	-0.081	0.615	0.147	0.36
VPW (mm)	-0.094	0.56	0.266	0.092
LVIDD (mm)	0.163	0.308	0.457	**0.003***
LVIDs (mm)	0.274	0.083	0.203	0.202
RWT (mm)	-0.275	0.082	0.003	0.985
IVRT	-0.143	0.372	0.208	0.191

FS: fractional shortening, , IVS: inter-ventricular septum, , LA: left atrium diameter, LPA: left pulmonary artery diameter, LVIDD: left ventricular internal diameter end diastole, LVIDS: left ventricular internal diameter end systole, LVMI: left ventricular mass index, LVPW: left ventricular posterior wall diameter, PA: main pulmonary artery diameter, RPA: right pulmonary artery diameter, r: Spearman rank correlation coefficient, RWT : regional wall thickness.

There were significant positive correlations between duration of therapy and both LV mass and LVIDD. there were non-significant correlations between duration of therapy and other parameters.

There were non-significant correlations between dose of therapy and any of M mode Echocardiographic data (Table 3).

Table (4): Correlation between percent of final height to lowest target height and M Mode Echocardiographic data:

	Percent of final height to ideal height	
	R	P
LV mass (g)	**-0.359**	**0.021***
LVMI (g/m^2)	**-0.349**	**0.025***
RWT	-0.031	0.846
FS (%)	0.16	0.316
PA (mm)	**-0.351**	**0.024***
RPA (mm)	-0.114	0.478
LPA (mm)	-0.009	0.957
AORTA (mm)	-0.27	0.088
LA (mm)	-0.151	0.347
IVS (mm)	-0.244	0.124
LVPW (mm)	-0.285	0.071
LVIDD (mm)	-0.302	0.055
LVIDs (mm)	-0.301	0.056
RWT (mm)	**0.355**	**0.023***

FS: fractional shortening, , IVS: inter-ventricular septum diameter, , LA: left atrium diameter, LPA: left pulmonary artery diameter, LVIDD: left ventricular internal diameter end diastole, LVIDS: left ventricular internal diameter end systole, LVMI: left ventricular mass index, LVPW: left ventricular posterior wall diameter, *p<0.05 is statistically significant, PA: main pulmonary artery diameter, RPA: right pulmonary artery diameter, r: Spearman rank correlation coefficient, RWT : regional wall thickness.

Statistically significant adverse associations existed between percent current height from target height and left ventricular mass, PA and left ventricular mass index. Statistically speaking, there was a strong association between percent current height from target height and RWT. There were non-significant correlations between percent current height to target height and other parameters (Table 4).

DISCUSSION

LV mass is generally presented as LV mass index (LVMI) where LV mass is indexed to body surface area allowing comparison of diverse patients with different statures [6].

We discovered an increase in left ventricular mass that was statistically significant (from 83.4 ± 32.18 to 89.57 ± 33.99 g) while there were significant increments in PA (from 18.89 ± 3.27 to 19.99 ± 3.71 mm), Aorta (from 23.25 ± 3.56 to 23.93 ± 3.0 mm), LVIDD (from 41.38 ± 6.66 to 42.89 ± 5.73) and LVIDs (from 26.03 ± 4.85 to 27.86 ± 4.84 mm). we reported a statistically non-significant change in LVMI, fraction shortening, RPA, LPA, LA, IVS, LVPW or RWT (Table 1) which indicates improvement in LV muscle mass and dimensions with GH therapy.

Patients with GHD have also reported substantial rhGH-induced increases in LV mass, cardiac output, and contractility. Increases in LV mass are related to changes in growth hormone levels or serum insulin-like growth factor-1 concentrations [7]. It is unclear whether growth hormone therapy would have a similar effect in patients with other GHD causes. Because the growth hormone receptor gene is expressed in the myocardium more strongly than in many other tissues, growth hormone therapy to hypophysectomized rats increases myocardial IGF-1 mRNA expression and myocardial IGF-1 levels other organs. expansion hormone-induced LV expansion in rats is primarily mediated by a growth in the size of myocardial cells. It's possible that growing myocardial cells won't always be advantageous [8].

By M-mode Echocardiography, **Ozdemir *et al.*** [3] showed that there were no discernible changes between the left aortic and atrial diameters, posterior wall and septum thickness, or LV shortening percentage during the course of the study (P>0.05). During rhGH therapy, the internal systolic dimensions of the left ventricle dramatically increased (21.4±2.63 to 24.0± 4.13 mm, P = 0.03). Diastolic dimensions also increased (36.5 ± 3.90 to 39.5 ± 4.94 mm, P<0.01). Left ventricular mass index increased throughout the study period (63.8 ± 27.1 to 79.3 ± 30.3 g/m^2, P<0.01).

On the other hand, it was shown that Children with GHD and short normal individuals did not have any changes in LV wall thickness, LV mass, or LV shortening percentage after receiving rhGH treatment. [9]. **Lanes *et al.*** [10] noted that teenagers with GHD, whether or not patients underwent rhGH therapy, did not seem to show alterations in cardiac mass and function or early atherosclerotic changes.

Richmond *et al.* [11] identified subclinical changes in the left ventricle's structure and function after a mean of 5 years of high dose rhGH treatment in kids with GHD, including an increase in mass and a decrease in the peak early velocity of the mitral valve. **Colao *et al.*** [12] found that 6 months after stopping rhGH therapy for GHD adolescents, the LV mass decreased, although not to subnormal levels, and that pre-withdrawal levels returned upon restarting rhGH medication. **Shulman *et al.*** [2] reported that infants with GHD may have difficulty growing their hearts, and that children receiving rhGH for the first time experienced a considerable rise in LV mass. **Salerno *et al.*** [13, 14] concluded that while GHD did not alter cardiac function in children, it significantly reduced cardiac size, which had an impact on heart morphology. Normalizing heart mass required rhGH replacement therapy for 12 to 2 years. **Capalbo *et al.*** [15] in their study demonstrated GHD was linked to anomalies in pediatric cardiac shape and function.

Gómez-Guzmán *et al.* [16] showed while being within acceptable ranges for age, the young people with GHD had significantly smaller LV systolic and diastolic dimensions than controls. Although the LV's diastolic diameter increased after 6 months of recombinant GH therapy, values for the LV's diastolic diameter were comparable to controls (p = 0.208).

The left ventricular (LV) mass, ejection fraction, and abnormal LV diastolic filling are frequently lowered in GHD patients. It has been shown that patients with GHD have thinner interventricular septum and posterior walls of the left ventricle. Additionally, a 14% significant drop in the LV ejection fraction was noted [17]. **Gola *et al.*** [18] revealed only a reduction in the LV posterior wall without any variations in LV internal diameter or ejection fraction between GHD patients and controls.

It was shown that cardiac dimensions after treatment, Compared to healthy controls, GHD patients had decreased left atrial and ventricular inner diameters, septal and posterior wall thickness, and left ventricular mass [19].

We found that there were statistically non-significant changes in LVMI, fractional shortening, RPA, LPA, LA, IVS, LVPW or RWT of our patients before and after r-hGH therapy (table 1).

Overall, it is suggested that cardiac size reduction is not a result of any biases in the measurement of LV mass but rather a result of having GHD. Studies on children with GHD's heart function have not been able to identify any abnormalities in cardiac function [12]. Ejection fraction and LV fractional shortening, the two most popular measures of systolic function, could not be

sensitive enough to pick up small variations in cardiac function. This is one of the main problems with measuring cardiac function by Echocardiography. LV fractional shortening and ejection fraction, which both heavily rely on myocardial loading, may overstate cardiac performance even if they may be helpful in a clinical environment.

A meta-analysis revealed that GH therapy significantly increased LV mass. This is most likely caused by the concurrent rise in LVEDD [20], verifying the majority of published trials' findings [21, 22], and in LVPW as demonstrated in previous studies [23, 24]. The extremely varying degree of basal LV mass impairment (and thus the potential increase during treatment) may be the cause of these variations in the impact of GH therapy on LV regional morphology. Indeed, the duration and severity of GHD differed from one study to another, as well as the proportion of patients with childhood-onset or adulthood-onset GHD [20].

Additionally, heterogeneous GH effects on cardiac output, fractional shortening, and the ejection fraction, which represents systolic function, have been documented. The slight elevation in cardiac output is most likely caused by an increase in heart rate and a rise in stroke volume, both of which have been seen in several experiments. Stroke volume was the only parameter in subgroup analyses of randomized trials that significantly increased, the reliability of this conclusion is constrained by the sparse number of trials and study populations. It is debatable if GH can boost contractility. Studies have suggested that fractional shortening has increased, whereas others showed no change [25].

Maison *et al.* [20] found that GH had a tendency to have a favorable impact on fractional shortening in their meta-analysis. It must be remembered that even if it does, Improved LV fractional shortening does not necessarily reflect increased contractility when loading parameters are constant. In fact, GH therapy was observed to improve both endothelium-dependent and non-endothelium-dependent vasodilatation, both of which were impaired in patients with GHD as compared to healthy control participants (26). Following GH treatment for GHD, LVEDD rises under preloading conditions, most likely as a result of the noticed rise in blood volume [27].

In children without a history of cardiac disease, retrospective studies found Over the course of two years of r-hGH therapy, neither the shape nor the function of the left ventricle changed (28). The conclusions that were reported by **Barton *et al.*** [29] differ from those reported in some GHD patients receiving r-hGH, who have recorded increases in left ventricular wall thickness and LVMI [21, 29]. According to some research, hormone replacement therapy can bring these values back to normal and reflect the myocardial atrophy linked to long-term GHD [21], Others have experienced a minor increase in their initially normal cardiac indices while maintaining their normal range [30]. The small rise in LVMI shown after two years of treatment with high dosage r-hGH falls within the 95% confidence interval for the assessment of mean LV mass for the numbers studied, according to the proven accuracy of M-mode Echocardiography in ideal conditions [31].

Barton *et al.* [29] demonstrated that after two years of treatment with r-hGH, the fractional shortening (FS) remained within the normal range (28-44%) and did not differ from controls. The 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 r-hGH groups after 2 years of therapy. With either r-hGH dose, no appreciable improvement in FS from baseline was seen after 1 or 2 years of treatment.

Barton *et al.* [29] also reported that the median (range) septal to posterior wall thickness was 1.2 (1.0-1.5) in 201U/m^2/week group and 1.0 (0.9-1.3) in 40 IU/m2/week group following two years of therapy (normal 1.3). Left ventricular mass index (LVMI) did not increase significantly with r-hGH in a dose of either 20 or 40 IU/m2/week throughout the first year of treatment. However, there was significant intra-individual variation in estimated LVMI across time, which would have obscured minute r-hGH-related changes. LVMI was comparable in each group at one year (P = 0.77). In patients receiving higher doses of r-hGH, there was a bigger increase in LVMI over the course of 2 years of treatment, but this did not achieve statistical significance (P = 0.4). After two years of treatment, LVMI was considerably greater than baseline values in those patients receiving 40 IU/ m2/week r-hGH (P = 0.04) but remained within the normal range [32], The measures of individuals who received 20 IU/m2/week of r-hGH did not significantly alter from baseline.

Gómez-Guzmán *et al.* [16] in their study showed that Following replacement therapy, the heart's size and LVM grew without having a negative effect on the diastolic function. Research has indicated that similar alterations to those reported can occur in just six months, however this hormone treatment produces immediate effects that do not appear to have been previously mentioned. It also coincides with the period of a greater increase in growth rate.

In **Minczykowski *et al.*** [33] study, they evaluated the heart's size and function before and after a year of treatment in GH-deficient patients, respectively. Eight of the patients in the study had an ejection fraction below 55%, demonstrating that GHD patients have cardiac dysfunction. After receiving GH treatment for a year, there was an increase in the ejection fraction along with a decrease in the left ventricular end-systolic volume, but

no appreciable change in the end-diastolic volume. **Losa *et al.* [34]** found that 42 months of GH treatment increased left ventricular mass and decreased atrial emptying index. When compared to healthy matched controls, a lower LV distensibility in proportion to LVH may be the reason for the decline in the LA emptying index, a measure of diastolic function. The results of the later trial may suggest that, despite the larger than usual amount of GH that was given, advanced age may increase a patient's vulnerability to experiencing an unjustified increase in left ventricular mass during long-term GH replacement therapy.

There were substantial favorable connections in the current study between the length of therapy and both LV mass and LVIDD. There were weak associations between the length of therapy and the other factors that were examined (table 3). The % of present height compared to desired height and both left ventricular mass and left ventricular mass index showed a statistically significant negative connection. There were statistically significant results positive correlation between percent current height from target height and RWT. We found non-significant correlation between percent current height to target height and other studied parameters (table 4).

CONCLUSION

LV mass increased remarkably in our patients after GH therapy .LV mass correlated positively with GH therapy's duration and adversely with the percentage of final height to lowest target height.

- **Sources of funding:** There was no particular grant from a public, commercial, or nonprofit funding organization for this research.
- **Conflicts of interest:** No conflicts of interest.

REFERENCES

,

2. **Shulman I, Root W, Diamond B *et al.* (2003):** Effects of one year of recombinant human growth hormone (GH) therapy on cardiac mass and function in children with classical GH deficiency. J Clin Endocrinol Metab., 88: 4095-9.
3. **Ozdemir O, Abaci A, Hizli S *et al.* (2011):** Cardiac functions in children with growth hormone deficiency before and during growth hormone-replacement therapy. Pediatr Cardiol., 32: 766-71.
4. **Roberson A, Cui W (2009):** Tissue Doppler imaging measurement of left ventricular systolic function in children: mitral annular displacement index is superior to peak velocity. J Am Soc Echocardiogr., 22:376–382
5. **Metwalley A, Farghaly S, Abd El-Hafeez A (2013):** Evaluation of left ventricular mass and function, lipid profile, and insulin resistance in Egyptian children with growth hormone defi ciency: A single-center prospective case-control study. Indian Journal of Endocrinology and Metabolism, (17): 876-882
6. **Lang M, Badano P, Mor-Avi V (2015):** Recommendations for cardiac chamber quantification by Echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr.*, *28*(1): 1-39.
7. **Amirpour A, Vakhshoori M, Zavar R *et al.* (2021):** The Effect of 3-Month Growth Hormone Administration and 12-Month Follow-Up Duration among Heart Failure Patients Four Weeks after Myocardial Infarction: A Randomized Double-Blinded Clinical Trial. Cardiovasc Ther., 3: 268-72.
8. **Rotwein P (2020):** Regulation of gene expression by growth hormone. Mol Cell Endocrinol., 507: 110-115.
9. **Tidblad A, Bottai M, Kieler H *et al.* (2021):** Association of Childhood Growth Hormone Treatment With Long-term Cardiovascular Morbidity. JAMA Pediatr., 175: 205-212.
10. **Lanes R, Gunczler P, Lopez E *et al.* (2001):** Cardiac mass and function, carotid artery intima-media thickness, and lipoprotein levels in growth hormone-deficient adolescents. J Clin Endocrinol Metab., 86: 1061-5.
11. **Richmond E, Rogol D (2010):** Current indications for growth hormone therapy for children and adolescents. Endocr Dev., 18: 92-108.
12. **Colao A, Di Somma C, Salerno M *et al.* (2002):** The cardiovascular risk of GH-deficient adolescents. J Clin Endocrinol Metab., 87: 3650-3655.
13. **Salerno M, Esposito V, Spinelli L *et al.* (2004):** Left ventricular mass and function in children with GH deficiency before and during 12 months GH replacement therapy. Clin Endocrinol (Oxf), 60: 630-636.
14. **Salerno M, Esposito V, Farina V *et al.* (2006):** Improvement of cardiac performance and cardiovascular risk factors in children with GH deficiency after two years of GH replacement therapy: an observational, open, prospective, case-control study. J Clin Endocrinol Metab., 91: 1288-1295.
15. **Capalbo D, Lo Vecchio A, Farina V *et al.* (2009):** Subtle alterations of cardiac performance in children with growth hormone deficiency: results of a two-year prospective, case-control study. J Clin Endocrinol Metab., 94, 3347-3355.
16. **Gómez-Guzmán E, Cañete D, Valle-Martos R *et al.* (2018):** Short-Term Evaluation of Left Ventricular Mass and Function in Children With Growth Hormone Deficiency After Replacement Treatment. Front Pediatr., 6: 174-178.
17. **Díez J, Sangiao-Alvarellos S, Cordido F (2018):** Treatment with Growth Hormone for Adults with Growth Hormone Deficiency Syndrome: Benefits and Risks. Int J Mol Sci., 19: 50-59.
18. **Gola M, Bonadonna S, Doga M *et al.* (2005):** Growth Hormone and Cardiovascular Risk Factors. J Clin Endocrinol Metab., 90: 1864-1870.
19. **Alkan F, Ersoy B, Kızılay O *et al.* (2021):** Cardiac functions in children with growth hormone deficiency: Effects of one year of GH replacement therapy. Growth Horm IGF Res., 60-61: 101-108.

20. **Maison P, Chanson P (2003):** Cardiac Effects of Growth Hormone in Adults With Growth Hormone Deficiency. Circulation, 108: 2648-2652.
21. **Amato G, Carella C, Fazio S *et al.* (1993):** Body composition, bone metabolism, and heart structure and function in growth hormone (GH)-deficient adults before and after GH replacement therapy at low doses. J Clin Endocrinol Metab., 77: 1671-1676.
22. **Carroll V, Christ R, Bengtsson A *et al.* (1998):** Growth hormone deficiency in adulthood and the effects of growth hormone replacement: a review. J Clin Endocrinol Metab., 83: 382-395.
23. **Ezzat S, Fear S, Gaillard C *et al.* (2002):** Gender-specific responses of lean body composition and non-gender-specific cardiac function improvement after GH replacement in GH-deficient adults. J Clin Endocrinol Metab., 87: 2725-2733.
24. **Verhelst J, Abs R (2002):** Long-term growth hormone replacement therapy in hypopituitary adults. Drugs, 62: 2399-2412.
25. **Stamatis V, Kontonika M, Daskalopoulos P *et al.* (2020):** Electrophysiologic Effects of Growth Hormone Post-Myocardial Infarction. Int J Mol Sci., 21: 150-156.
26. **Evans L, Davies J, Anderson R *et al.* (2000):** The effect of GH replacement therapy on endothelial function and oxidative stress in adult growth hormone deficiency. Eur J Endocrinol., 142: 254-262.
27. **Tidblad A, Bottai M, Kieler H *et al.* (2021):** Association of Childhood Growth Hormone Treatment With Long-term Cardiovascular Morbidity. JAMA Pediatr., 175: 205-209.
28. **Rowland W, Morris H, Biggs E *et al.* (1991):** Cardiac effects of growth hormone treatment for short stature in children. J Pediatr Endocrinol Metab., 4: 19-24.
29. **Barton S, Gardineri M, Cullen S *et al.* (1995):** The growth and cardiovascular effects of high dose growth hormone therapy in idiopathic short stature. Clin Endocrinol (Oxf), 42: 619-26.
30. **Cuneo C, Salomon F, Wilmshurst P *et al.* (1991):** Cardiovascular effects of growth hormone treatment in growth-hormone-deficient adults: stimulation of the renin-aldosterone system. Clin Sci (Lond), 81: 587-592.
31. **Devereux B (1987):** Detection of left ventricular hypertrophy by M-mode Echocardiography. Anatomic validation, standardization, and comparison to other methods. Hypertension, 9: 19-26.
32. **Daniels R, Meyer A, Liang C *et al.* (1988):** Echocardiographically determined left ventricular mass index in normal children, adolescents and young adults. J Am Coll Cardiol., 12: 703-708.
33. **Minczykowski A, Gryczynska M, Ziemnicka K *et al.* (2005):** The influence of growth hormone (GH) therapy on cardiac performance in patients with childhood onset GH deficiency. Growth Horm IGF Res., 15: 156-164.
34. **Losa M, Von Werder K (2001):** The Heart in Acromegaly. In: GIUSTINA, A. & MANELLI, F. (eds.) Growth Hormone And The Heart. Boston, MA., Springer US.