

## Metabolic and Cardiac Effects of Growth Hormone Therapy in Children with Turner Syndrome

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### ABSTRACT

**Background:** Turner Syndrome (TS) is the most frequent genetic defect in females. TS patients are characterized by growth failure, metabolic and cardiovascular abnormalities. **Objective:** The study aimed at determining the influence of growth hormone (GH) therapy on TS patients' body composition, metabolic profile, and cardiac functioning.

**Patients and methods:** This clinical trial comprised 54 TS females divided into two subgroups; 29 TS females on GH medication  $\geq 6$  months (interventions) made up Group 1 and 25 TS females who didn't start treatment were in Group 2 (controls). Ages were between 6.01 and 17.1 years. Anthropometric measures, skin fold thickness measurements, body composition analysis and blood pressure were recorded. Fasting levels for lipids, blood glucose, and C-peptide were measured. Tissue Doppler Imaging (TDI), M-mode, complete two-dimensional, and Pulsed-Wave Doppler Echocardiography were performed.

**Results:** Patients with TS receiving GH therapy had significantly higher high density lipoprotein cholesterol (HDL-C), waist circumference (WC) for age, hip circumference, bone mass and impaired global myocardial function. Positive correlation between the age of initiating GH therapy and triglyceride levels were observed while negative correlation with height for age and muscle percentage. Homeostatic model assessment-insulin resistance (HOMA-IR) demonstrated a positive relationship with WC and the sum of skin fold thickness percentiles.

**Conclusion:** GH increases HDL-C, WC and bone mass. Increased WC and skinfold thickness are insulin resistance risk factors. Earlier age of patient at start of GH therapy is connected with decreased triglyceride levels and a higher muscle percentage. TDI detected impairment of global myocardial function of both ventricles.

**Keywords:** Body composition, Growth hormone, Metabolic profile, Myocardial function, Turner Syndrome, Clinical trial, Cairo University.

### INTRODUCTION

Turner Syndrome (TS) is a female-specific genetic disease. It is distinguished by the full or partial deletion of one of the X chromosomes. The incidence is around 1:2500 live births. Diagnosis is based on performing karyotyping including at least 30 cells<sup>(1)</sup>. TS is associated with several developmental and health issues including growth failure, streak gonads and cardiovascular abnormalities<sup>(2)</sup>.

Females with TS are shorter and heavier when compared to their healthy peers. They are more prone to cardiovascular events and to developing metabolic abnormalities<sup>(3)</sup>.

Growth hormone (GH) therapy is used in females with TS to improve predicted adult height. It also has effects on metabolic parameters and cardiovascular functions<sup>(4)</sup>. GH's effects on TS patients' glucose tolerance and insulin resistance (IR) were studied but results were controversial<sup>(1)</sup>. Some studies did not observe any negative effect of GH therapy on glucose homeostasis<sup>(5,6)</sup> despite deterioration in insulin sensitivity in a number of those studies<sup>(7,8)</sup>.

Multiple studies found that starting GH medication improved lipid profiles in females with TS. LDL

cholesterol (LDL-C) and total cholesterol are reduced by GH, whereas triglycerides (TG) and HDL cholesterol (HDL-C) are increased<sup>(1,9)</sup>.

It also has beneficial impacts on body composition, reducing total body fat and increasing lean mass<sup>(10)</sup>.

Assessment of GH therapy's impact on heart dimensions and functions using conventional echocardiography had been investigated by several researchers. They stated that echocardiography revealed no abnormalities in heart dimensions, LV or RV systolic or diastolic functions<sup>(11,12)</sup>.

The effect of GH therapy on heart function in females with TS has been studied using modern techniques such Tissue Doppler Imaging (TDI). Results are controversial. TDI, according to some studies, can detect systolic and diastolic problems earlier than traditional echocardiography<sup>(13)</sup>.

Other studies revealed that myocardial function did not differ prior to and following the use of GH replacement<sup>(11)</sup>.

The study aimed at determining the influence of GH therapy on TS patients' body composition, metabolic parameters and cardiovascular functions and dimensions.

## PATIENTS AND METHODS

The participants in this clinical trial included 54 TS-positive females. Both classic and non-classic patients with TS aged  $\geq 6$  years were included. Participants were divided into 2 groups. The first group comprised 29 TS females who had been undergoing GH therapy for  $\geq 6$  months (intervention). Group 2 included 25 patients with TS before initiating GH therapy (controls).

Patients with thyroid abnormalities, diabetes mellitus before start of GH treatment or history of acquired heart conditions (e.g., rheumatic fever or viral myocarditis), on chronic medications such as corticosteroids or those on GH treatment  $< 6$  months (for *Group 1*) were excluded.

All included subjects were evaluated by Full History-Taking including age and age at presentation. For those on GH therapy, age at initiation of therapy, dose (mg/kg/day) and duration of therapy were recorded.

A Full Clinical Examination was carried out, which included weight (recorded to the closest 0.1 kg using an electronic scale). A stadiometer is used to determine height in centimeters and body mass index (BMI) is calculated. Waist and hip circumferences were recorded using a tape to 0.1 cm accuracy. Waist hip ratio (WHR) and waist circumference (WC) values for Dutch children were used to compute standard deviations <sup>(14)</sup>. Skin fold thickness was recorded in mms on the right side of the body 3 times using a skinfold caliper (Digital Body Fat Caliper) and the average was calculated. Measurements were taken over triceps, biceps, subscapular and supriliac regions. The total thickness of the 4 skin folds was plotted on percentiles curves of Turkish children <sup>(15)</sup>. Body Composition Analysis was done using an electronic scale (Beurer BF 100 Body Complete, Beurer GmbH, Soflinger Str.218, 89077Ulm, Germany). It calculates the bone mass (kg) and the percentages of lean body mass, total body water and total body fat.

A standardized mercury sphygmomanometer was used to measure blood pressure (BP) 3 times in the sitting position with an appropriate cuff and defined as normal or increased according to updated definitions of BP categories and stages <sup>(16)</sup>.

Laboratory investigations: Blood samples drawn after a 12-14 hour fast were analyzed within 6 hours for: Lipid profile (Total cholesterol, LDL-C, HDL-C and TG), fasting insulin, fasting c-peptide and fasting blood glucose.

Thyroid hormones (TSH, FT3 and FT4) were measured (chemiluminescence immunoassay-Abott Diagnostics Architect) to exclude thyroid dysfunction as well as liver enzymes [ aspartate aminotransferase (AST) and alanine aminotransferase (ALT), semi or fully automatic analysers based on photometry which measures light absorbed in UV-visible-infrared range. Beer-Lambert law is used to calculate coefficients].

The following parameters were calculated using fasting insulin and glucose levels:

- Homeostatic model assessment-insulin resistance (HOMA-IR) = [fasting insulin ( $\mu$  U/ml) x fasting glucose (mg/dl)]/405. Insulin resistance is considered if  $> 2.5$ .

- Glucose/insulin ratio. Insulin resistance is considered if  $< 4.5$ .

Conventional and Tissue Doppler Echocardiography: Transthoracic Echocardiography with probe frequencies adequate for patient size was performed using the Vivid S5 N equipment from GE Vingmed Ultrasound AS, Strandpromenaden 45, N-3191 Horten, Norway.

*Two-dimensional (2D) and Motion Mode (M mode) Echocardiography:* Interventricular septum thickness in end-diastole (IVSD), posterior wall thickness in diastole (PWd), and fractional shortening (FS) were all measured using the parasternal long-axis view <sup>(17)</sup>. Tricuspid annular plan systolic excursion (TAPSE) and mitral annular plan systolic excursion (MAPSE) were measured in an apical 4 chamber view at the tricuspid annulus and the septum's basal part <sup>(18)</sup>.

*Pulsed Wave Doppler Echocardiography:* E/A ratio determined from the 4-chamber apical view at the tip of the mitral leaflets <sup>(18)</sup>.

*Tissue Doppler Imaging:* To begin the investigation, the tissue velocity mode was chosen. Systolic (S') and peak early diastolic (E') velocities were measured using Pulsed Wave Tissue Doppler Imaging (PW-TDI) in the basal segments of LV's posterior and septal walls, as well as the RV's anterior wall <sup>(20)</sup>. PW-TDI was used to calculate the global myocardial performance index (MPI): interval measurements were taken during a single cardiac cycle. MPI was computed as MPI= isovolumetric contraction time (ICT) + isovolumetric relaxation time (IRT)/ ejection time (ET) for RV MPI using PW-TDI at the tricuspid annulus and LV MPI at the lateral mitral annulus using PW-TDI <sup>(21)</sup>.

### **Ethical approval:**

**This study was approved by the Ethical Committee Institutional Review Board (IRB) of Kasr Alainy Medical School, Cairo University prior to patients' enrollment. All patients became enrolled in the study after an expressed written approval that was obtained from parents. This study was executed according to the code of ethics of the World Medical Association (Declaration of Helsinki) for studies on humans.**

### *Statistical analysis*

SPSS (Statistical Package for the Social Sciences; SPSS Inc., Chicago, IL, USA) version 21 for Microsoft Windows was used for all statistical calculations. Qualitative data were defined as numbers and percentages. Chi-Square test and Fischer exact test were used for comparison between categorical variables as appropriate. Quantitative data were tested for normality

by Kolmogorov-Smirnov test. Normal distribution of variables was described as means and SD, and independent sample t-test/Mann Whitney U test was used for comparison between groups. Paired t test was used to compare numerical variables within groups when comparing two groups. Analysis of correlation (using Pearson's method): to determine how strongly two quantitative variables are associated. P value  $\leq 0.05$  was considered to be statistically significant.

**RESULTS**

This clinical trial comprised 54 females with TS with ages ranging from 6.01-17.1 years (mean 11.84 and SD 3.11). They were divided into two subgroups as follows:

Group 1 had 29 participants with TS receiving GH therapy. The mean age at initiation of GH was 9.95 (SD 3.39) years old and the duration of therapy was 2.47 (SD 2.14) years. Dose of GH used was 0.45 mg/kg/day.

Group 2 had 25 participants with TS before initiation of GH therapy (controls) matched for age, weight, height and BMI.

Despite matching in age, weight, height, and BMI, Group 1 had substantially greater waist circumference, waist circumference SDS, and hip circumference than Group 2 (P values 0.012, 0.03, and 0.019, respectively). Other demographic information and anthropometric measurements are summarized in **Table 1**.

**Table 1:** Comparison between the 2 groups regarding demographic data, anthropometric measurements and various body measurements.

Variable	Group 1 (N= 29) (Mean $\pm$ SD)	Group 2 (N= 25) (Mean $\pm$ SD)	P value
Age (years)	12.43 $\pm$ 3.06	11.16 $\pm$ 3.08	0.12
Age at presentation (years)	7.72 $\pm$ 4.63	8.50 $\pm$ 4.24	0.66
Height percentiles for age using TS growth percentiles	60.19 $\pm$ 26.96	46.74 $\pm$ 22.94	0.79
Weight SDS for height	3.66 $\pm$ 2.53	3.05 $\pm$ 3	0.38
Target height SDS	-0.45 $\pm$ 0.84	-0.55 $\pm$ 0.81	0.69
Projected height (cm)	143.73 $\pm$ 7.38	140.88 $\pm$ 7.86	0.29
BMI SDS	1.22 $\pm$ 1.03	0.63 $\pm$ 1.4	0.096
WC (cm)	69.93 $\pm$ 11.89	61.58 $\pm$ 10.87	0.012*
WC SDS for age	0.87 $\pm$ 1.24	-0.12 $\pm$ 1.82	0.03*
HC (cm)	77.93 $\pm$ 12.25	69.72 $\pm$ 11.46	0.019*
WHCR	0.897 $\pm$ 0.46	0.88 $\pm$ 0.06	0.296
WHCR SDS for age	1.52 $\pm$ 0.75	1.02 $\pm$ 1.12	0.11

BMI: body mass index; SD: standard deviation; TS: turner syndrome. HC: Hip circumference; WC: Waist circumference; WC SDS: Waist circumference standard deviation score; WHCR: Waist hip circumference ratio; WHCR SDS: Waist hip circumference ratio standard deviation score.

Additionally, Group 1 had much higher bone mass. The variance in systolic and diastolic blood pressure readings between the two subgroups was not statistically significant (**Table 2**).

**Table 2:** Comparison between the 2 groups regarding Sum of skin fold thickness percentiles, body composition analysis and blood pressure.

Variable	Group 1 (N= 29) (Mean $\pm$ SD)	Group 2 (N= 25) (Mean $\pm$ SD)	P value
Sum of skin fold thickness percentiles	49.07 $\pm$ 28.22	40.14 $\pm$ 31.24	0.32
Fat %	22.92 $\pm$ 7.01	21.96 $\pm$ 7.29	0.71
Muscle %	43.02 $\pm$ 8.59	47.01 $\pm$ 8.95	0.17
Water %	58.05 $\pm$ 8.65	59.65 $\pm$ 10.04	0.54
Bone (kg)	8.28 $\pm$ 1.37	7.22 $\pm$ 1.03	0.00*
Systolic blood pressure (mmHg)	107.83 $\pm$ 14.5	110.2 $\pm$ 10.46	0.47
Diastolic blood pressure (mmHg)	71.83 $\pm$ 11.73	76.96 $\pm$ 9.19	0.12

*N.B:* Sum of skin fold thickness percentiles is the sum of biceps, triceps, subscapular and suprailiac skin fold thickness.

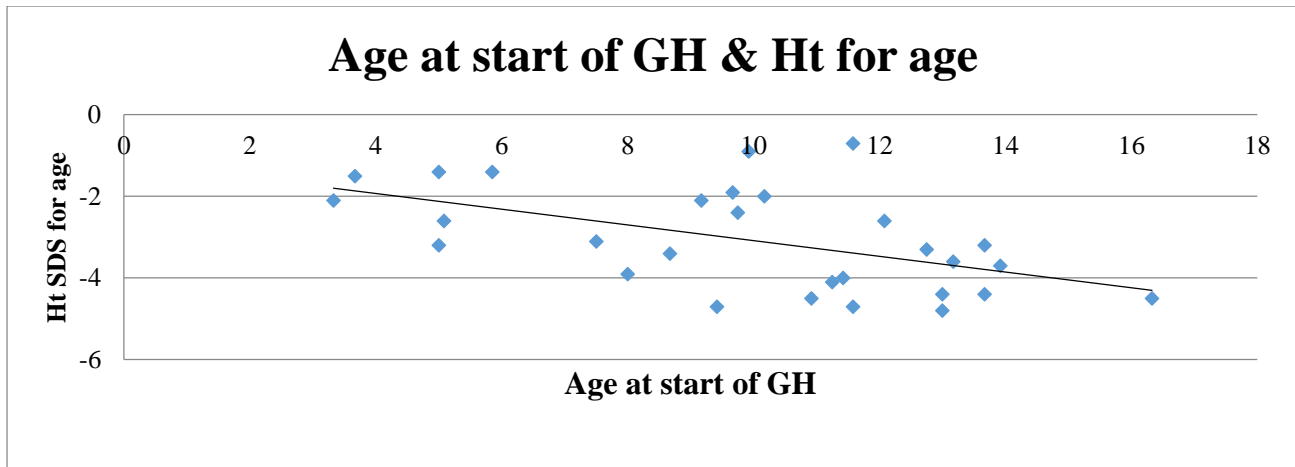
Group 1 had considerably greater HDL levels than Group 2, but there were no statistically significant differences regarding cholesterol, LDL-C, TG, AST, ALT, fasting serum insulin, fasting c-peptide, fasting blood glucose, HOMA-IR, or glucose/insulin ratio (**Table 3**).

**Table (3):** Metabolic Derangements in both groups:

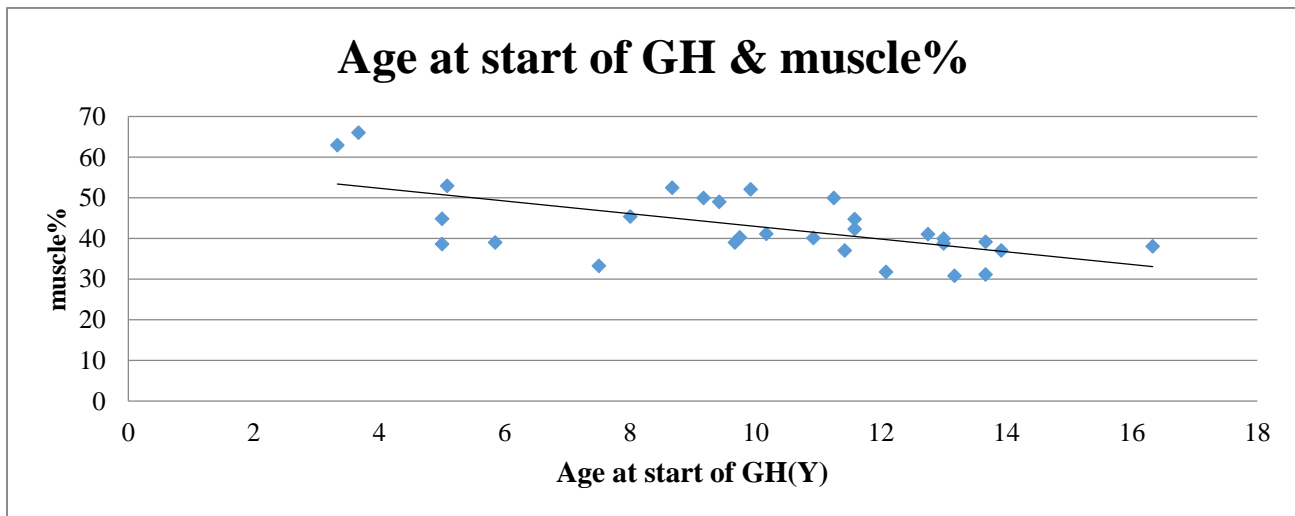
Variable	Group 1 (N= 29) (Mean ± SD)	Group 2 (N= 25) (Mean ± SDS)	P value
Cholesterol mg/dl	172.79 ± 29.01	170.56 ± 29.71	0.34
LDL mg/dl	98.72 ± 13.24	112.38 ± 19.64	0.97
HDL mg/dl	57.28 ± 4.25	46.37 ± 8.9	0.004*
TG mg/dl	88.76 ± 5.65	90.46 ± 3.87	0.68
ALT mg/dl	26.41 ± 5.2	22.52 ± 7.73	0.9
AST mg/dl	26.17 ± 4.86	27.2 ± 3.78	0.58
Fasting serum insulin (uIU/ml)	13.16 ± 1.55	11.66 ± 1.26	0.15
Fasting c- peptide (ng/ml)	1.89 ± 0.16	1.73 ± 0.15	0.47
Fasting blood glucose (mg/dl)	81.17 ± 11.11	84.46 ± 8.31	0.33
HOMA-IR	2.91 ± 0.7	2.51 ± 0.33	0.15
G/I ratio	10.08 ± 2.15	14.9 ± 1.51	0.08

ALT: alanine aminotransferase; AST: aspartate aminotransferase; HDL: high density lipoprotein; LDL: low density lipoprotein; TG: triglycerides; G/I ratio: glucose insulin ratio; HOMA-IR, homeostatic model assessment-insulin resistance.

The following correlations were observed in Group 1: The patient's height (Ht) was negatively associated to the age at which GH medication was commenced ( $r = -0.525$ ,  $P = 0.003$ ), as well as muscle percentage ( $r = -0.62$ ,  $P = 0.000$ ) (Figures 1 and 2).



**Figure 1.** Correlation between age of patient at start of GH therapy and Ht.



**Figure 2.** Correlation between age of patient at start of GH therapy and muscle percentage.



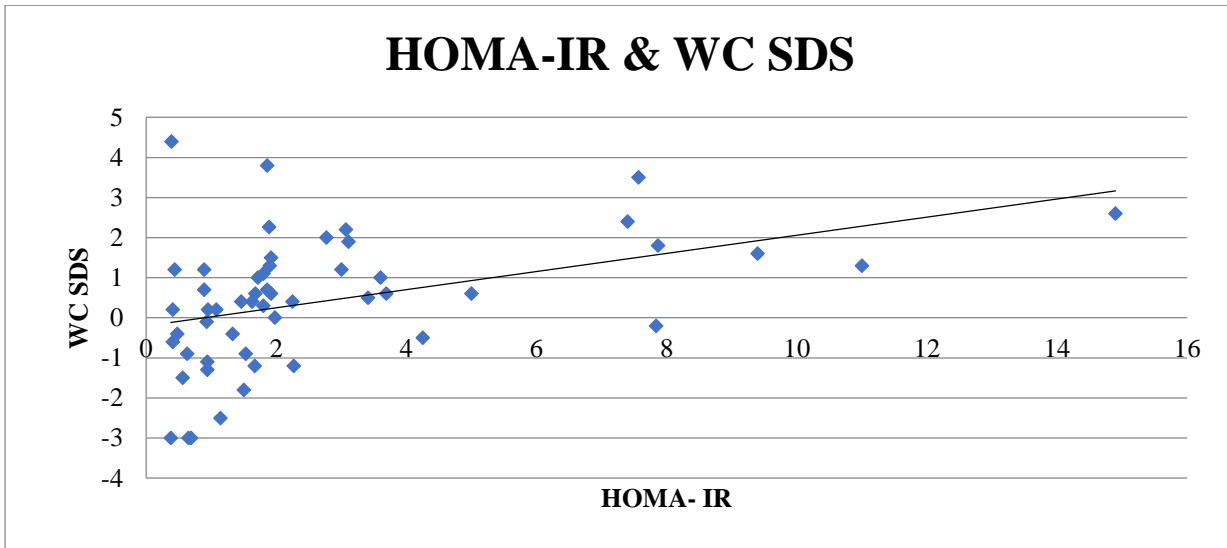


Figure 5. Correlation between HOMA-IR and WC.

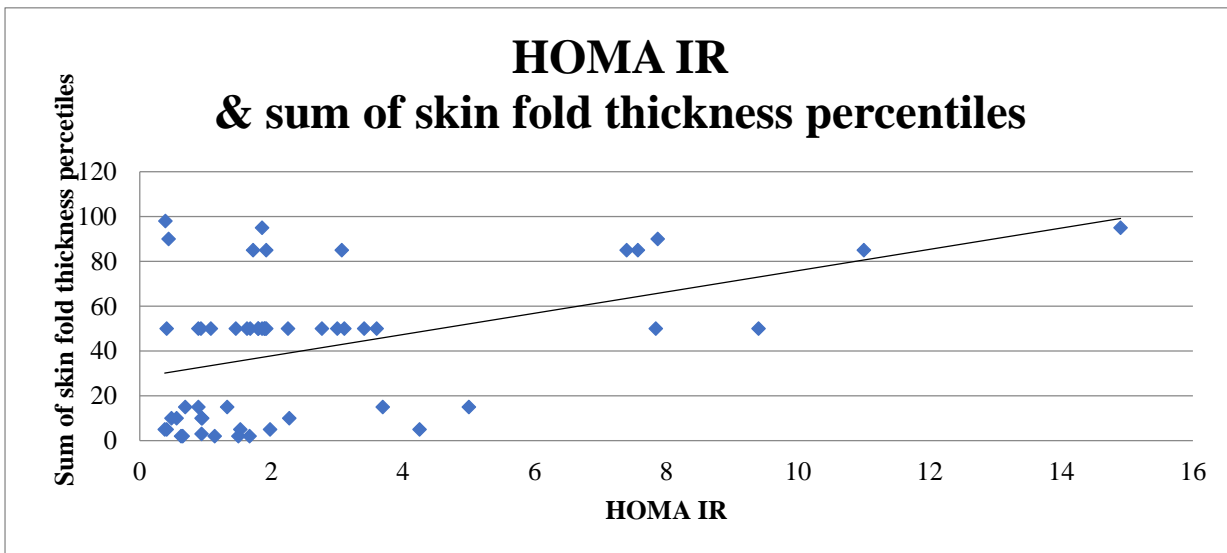


Figure 6. Correlation between HOMA-IR and sum of skin fold thickness percentiles.

Echocardiographic measures revealed no statistically significant variations in IVSd, PWd, FS %, TAPSE, MAPSE, or E/A ratio between Groups 1 and 2 (Table 4).

Table (4): Conventional Echocardiographic parameters in the two groups:

Variable	Group 1 (N= 29) (Mean ±SD)	Group 2 (N= 25) (Mean ± SD)	P value
IVSd (cm)	0.75 ± 0.21	0.68 ± 0.15	0.296
PWd (cm)	0.71 ± 0.2	0.6 ± 0.12	0.053
FS%	39.82 ± 5.23	38.96 ± 5.9	0.4
TAPSE (cm)	2.01 ± 0.31	1.88 ± 0.32	0.18
MAPSE (cm)	1.45 ± 0.29	1.4 ± 0.19	0.71
E/A ratio	1.56 ± 0.35	1.63 ± 0.38	0.39

A: peak atrial diastolic flow velocity; E: peak early diastolic flow velocity; FS: fractional shortening; IVSD: inter-ventricular septum thickness in end diastole; MAPSE: mitral annular plane systolic excursion; PWd: posterior wall thickness in diastole; TAPSE: tricuspid annular plane systolic excursion.

However, utilizing Tissue Doppler Imaging, Group 1 revealed a greater left and right ventricle myocardial performance index, as well as an S' wave in the LV septal wall, than Group 2, with highly statistically significant variances (P values 0.006, 0.000, and 0.002, respectively). On the other hand, there were no statistically significant variances regarding S'; wave in anterior walls of the RV and posterior walls of the LV, or E' wave in anterior walls of the RV, septal and posterior walls of LV (Table 5).

**Table 5.** Tissue Doppler Imaging parameters in the two groups.

Variable		Group 1 (n=29) (Mean ± SD)	Group 2 (n=25) (Mean ± SD)	P value
LV modified MPI		0.53 ± 0.25	0.35 ± 0.14	0.006*
RV modified MPI		0.499 ± 0.18	0.33 ± 0.09	0.000*
LV S' (mm/s)	Septal wall	76.7 ± 13.8	66 ± 13.56	0.002*
	Posterior wall	81.78 ± 21.98	69.88 ± 20.09	0.09
RV S' of anterior wall (mm/s)		125.7 ± 26.75	114.71 ± 31.06	0.57
LV E' (mm/s)	Septal wall	124.44 ± 21.4	116.67 ± 20.75	0.32
	Posterior wall	156 ± 34.3	146.54 ± 36.65	0.35
RV E' of anterior wall (mm/s)		153.93 ± 28.97	148 ± 30.94	0.43

E', peak early diastolic velocity; LV, left ventricle; MPI, global myocardial performance index; RV, right ventricle; S', systolic velocity.

## DISCUSSION

GH therapy in females with TS affects their growth and development. It also positively impacts body composition, muscle strength, bone mineral density and cardiovascular system<sup>(3)</sup>. However, it may alter glucose metabolism<sup>(22)</sup>. The study's goal was to see how GH therapy affected girls with TS's body composition, metabolic profile, and cardiovascular functions and dimensions. Participants in both groups were age, weight, and BMI matched.

Owing to the fact that utilizing GH improves final adult height, The GH therapy group outgrew the control group in height. However, the difference was statistically insignificant<sup>(3)</sup>. This could be explained by the short duration of GH therapy. Similarly, Group 1 had a higher projected height than Group 2, even though the variance was not statistically significant.

In Group 1, the older the patients at the onset of GH therapy, the shorter they were during the course of this research ( $r = -0.525$ ,  $P = 0.003$ ). 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<sup>(23)</sup>.

The first group had significantly more bone mass than the second group ( $P < 0.001$ ). This is owing to GH's beneficial influence on bone development, which is mediated through insulin-like growth factor-1 (IGF-1)<sup>(24)</sup>.

The two subgroups did not statistically differ in body muscle%. Initial data of muscle mass percentage before initiating GH in *Group 1* was not available for comparison. However in *Group 1*, there was a significant inverse correlation between age at GH therapy initiation and muscle mass percentage. This is explained by the beneficial effect of GH therapy through IGF-1<sup>(3,24)</sup>.

Other body composition indicators, such as fat and water percentages, did not show statistically significant variances between the two subgroups. A longer period of follow-up is necessary to demonstrate

the impact of growth hormone treatment on several body composition markers<sup>(10,25,26)</sup>.

Both groups' systolic and diastolic blood pressure values were comparable. It is estimated that 24-40% of adults with TS are at risk of developing hypertension. Researchers observed that GH therapy does not cause hypertension in females with TS<sup>(12,27,28)</sup>.

Patients with GH deficiency are more prone to develop lipid disorders and treatment with GH has a positive impact on the lipid profile of females with TS<sup>(29)</sup>. Several studies detected a significant decrease in total cholesterol<sup>(9)</sup> and LDL cholesterol<sup>(26)</sup> after initiating GH therapy, and a considerable rise in HDL cholesterol<sup>(26,29)</sup>, but no triglyceride alterations<sup>(26)</sup>.

Group 1 had significantly greater HDL levels than Group 2 in the current study ( $57.28 \pm 14.25$  mg/dl versus  $46.37 \pm 8.9$  mg/dl,  $P = 0.004$ ). TG levels correlated positively with the age at initiation of GH therapy; however, TC levels were comparable in both groups. When compared to the control group, LDL and TG values in the GH-treated group were lower. Although it was not statistically significant, this could be owing to a data shortage on these individuals' lipid profiles prior to starting GH medication, which might have been greater.

Greater cholesterol levels have been linked to higher diastolic blood pressure ( $r = 0.32$ ,  $P = 0.044$ ). A study of 60 Type 2 Diabetes patients discovered that cholesterol levels correlated positively with diastolic blood pressure<sup>(30)</sup>.

Alterations in glucose metabolism are observed in around 70% of females with TS<sup>(31)</sup>. Impaired glucose tolerance, elevated insulin levels and reduced insulin sensitivity could be detected. These abnormalities are aggravated using GH therapy. The use of GH disrupts normal insulin signaling resulting in abnormal metabolism, decreased glucose uptake by muscles and increased liver production<sup>(22)</sup>.

In the current work, the two subgroups did not significantly differ in fasting glucose and serum insulin levels, HOMA-IR, or glucose/insulin ratio. An earlier study investigated GH's effects on glucose, lipid, and protein metabolism in TS patients. No significant

change in HOMA-IR during treatment was detected<sup>(26)</sup>. This could be explained by the short duration of GH therapy.

In our study, HOMA-IR correlated positively with WC and the total thickness of skin folds ( $r=0.416$ ,  $P=0.002$  and  $r=0.474$ ,  $P=0.001$ , respectively). Increased WC and skin fold thickness are significant risk factors for developing insulin resistance<sup>(32)</sup>.

The two groups did not differ considerably in the interventricular septum and posterior wall dimensions. Several studies observed that GH therapy did not affect the cardiac dimensions in females with TS<sup>(33,34)</sup>.

There were no significant variations in the left ventricular systolic and diastolic functions, as well as the RV systolic functions, between Groups 1 and 2.

LV global systolic functions assessed using fractional shortening (FS), LV longitudinal systolic function assessed using Mitral Annular Plane Systolic Excursion (MAPSE), the RV longitudinal systolic function represented by tricuspid annular plane systolic excursion (TAPSE) and the LV diastolic functions using the E/A ratio). Researchers observed that using GH therapy does not affect LV or RV systolic function and diastolic function<sup>(11,12)</sup>.

Assessment of global myocardial function by measuring modified MPI of LV and RV using Tissue Doppler Imaging was done in the present study. This demonstrated that Group 1 had significantly higher LV modified MPI, and RV modified MPI than Group 2 (Group 1:  $0.53\pm0.25$  versus Group 2:  $0.35\pm0.14$ ) and RV (Group 1:  $0.499\pm0.18$  versus Group 2:  $0.33\pm0.09$ ), respectively. This indicates impaired global (both systolic and diastolic) function in GH-treated cases. That impairment was not apparent by conventional echocardiography. This necessitates using more advanced techniques to assess cardiac functions (e.g., Tissue Doppler Imaging which is a form of echocardiography that measures the velocity of the heart muscle cells rather than blood flow velocities used in traditional echocardiography).

Tissue Doppler Imaging was also utilized to determine myocardial velocities (peak systolic velocity (S'), early diastolic velocity (E') at the basal segments of LV septal and posterior walls and RV anterior wall. Except for the peak systolic velocity (S') of the LV septal wall, no statistically significant changes were found. Group 1 had a greater level than Group 2 ( $76.7\pm13.8$  mm/s versus  $66\pm13.56$  mm/s) indicating pressure-overload and explains some degree of diastolic dysfunction. GH increases cardiac mass and this in turn may affect diastolic function<sup>(15)</sup>. These subtle yet significant changes occurring may be detected using MPI rather than other parameters. In contrast, a group of researchers used Tissue Doppler Echocardiography to compare LV and RV diastolic functions before and after GH replacement in children with GH deficiency

and found no significant variation in myocardial diastolic function<sup>(11)</sup>.

In Group 1, affection of cardiac function was apparent using MPI (combined measurements of both systolic and diastolic function) rather than measuring a single systolic or diastolic function parameter. More research is required to investigate the early impact of GH replacement on heart function.

**Study limitations** include a small sample size, prospective study within the same subjects and the unavailability of Egyptian SDS scores for the waist circumference and waist hip ratios in addition to the percentile curves for the skin fold thickness.

## CONCLUSION

GH increases HDL-C, WC and bone mass. Increased WC and skinfold thickness are risk factors for insulin resistance. The earlier age of patients at the start of GH therapy relates to decreased triglyceride levels and a larger muscle proportion. Impairment of global myocardial function of both ventricles was detected using Tissue Doppler Imaging but not conventional echocardiography. Further studies using advanced techniques are required for detecting early abnormalities in cardiac function.

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**Conflict of Interest:** None.

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