Left ventricular diastolic function abnormalities in hypopituitary patients with GH deficiency: Evidence for a subclinical cardiomyopathy

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ABSTRACT. The aim of this study was to evaluate cardiac performance, in particular diastolic function, in adult patients with adulthood onset GH deficiency. The study group was composed of 19 GH deficient adult hypopituitary patients with atleast 3 additional pituitary hormone deficits and 19 age, sex and BMI matched healthy controls. Mean duration of hypopituitarism was 108.6±77.0 months. None of the patients and controls presented with or had previous diagnosis of concomitant diseases that could affect cardiac function. All hormone deficiencies, except for GH, were appropriately replaced in the patients. Left ventricular function and geometry were evaluated by two-dimensional, M-mode and Doppler echocardiography. Body composition was evaluated by bioelectrical impedance analysis. Not significant differences were observed with respect to left heart dimensions and left ventricular systolic function between patients and controls. Nevertheless 2 of the left ventricular diastolic function parameters, deceleration time and isovolumetric relaxation time, were significantly prolonged in the patients compared with controls (247.88± 70.65 *vs* 143.26±31.70 milliseconds (ms) and 122.31±18.24 *vs* 89.47±12.12 ms respectively, $p<0.001$). Duration of hypopituitarism was significantly correlated with percent body fat mass ($r=0.6119$, $p<0.01$) and percent lean body mass ($r=-0.5949$, $p<0.01$). It is concluded that in adults affected by hypopituitarism, GH deficiency predominantly impairs diastolic function while systolic function at rest is spared. This observation might indicate a preclinical stage of a cardiomyopathy. (J. Endocrinol. Invest. *25:* 590-597, 2002)

INTRODUCTION

It is well known that a long-term excess of GH causes cardiac hypertrophy and diastolic and systolic functional abnormalities (1, 2). Conversely, GH deficiency in adults also leads to impairment of heart structure and functions (3, 4). A form of cardiomyopathy specifically related to GH deficiency was formerly described (5, 6). In one of these patients, endomyocardial biopsy indicated a marked decrease of cardiac myofibrils (decreased ratio of myofibrillar volume to cell volume), a finding which was reversed after 3 months of GH treatment (5). Previous studies determining cardiac structure and function in asymptomatic hypopituitary patients indicated decreased myocardial mass and systolic dysfunction particularly in childhood onset GH deficiency (3, 4). Most (7-12), but not all (13), of the studies reported no differences in cardiac mass or systolic function between adulthood onset GH deficient patients and healthy subjects.

It is reported that abnormalities of diastolic function have a major role in producing signs and symptoms of cardiac dysfunction (14). The incidence of diastolic dysfunction is age-related and heart failure due to diastolic dysfunction rises dramatically with age (15). Doppler echocardiography has been accepted as a reliable, reproducible and noninvasive method for diagnosis and follow-up of patients with diastolic dysfunction (14). In hypopituitary patients a more limited number of studies investigated diastolic function parameters (7-9, 12, 16).

The aim of this study was to determine cardiac per-

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formance, in particular diastolic function, in adult patients with adulthood onset GH deficiency due to hypothalamic pituitary disease.

MATERIALS AND METHODS

19 hypopituitary adults with at least 3 pituitary hormone deficiencies other than GH and 19 normal subjects participated in the study. The patients and controls were matched for age, sex and BMI (Table 1). Patients were recruited from the Endocrine Clinic of Internal Medicine of the Istanbul Faculty of Medicine. Controls were recruited from hospital staff and friends. The study was performed according to the Declaration of Helsinki.

Causes of hypopituitarism were pituitary tumors treated by surgery, by radiotherapy, or by both in 12 patients, Sheehan's syndrome in 5 patients and primary empty sella in 2 patients. Mean duration of hypopituitarism was 108.6±77.0 months (median 84). All patients were on conventional replacement therapy consisting of L-T_4, glucocorticoids, sex hormones (except for post-menopausal women) and desmopressin where necessary. Three patients were post-menopausal. In the control group, 3 women were also post-menopausal (*p*=NS). Other women of the control group had regular menstrual cycles. None of the post-menopausal women of the control group was receiving sex hormone preparations. GH treatment was not previously given to any of the patients. All patients were stable on conventional replacement treatment for at least 6 months before the study. None of the patients and controls presented with or had previous diagnosis of concomitant diseases such as ischemic cardiovascular disease, diabetes mellitus or hypertension which could affect cardiac function and no medication other than conventional replacement therapy for hypopituitary group was given to the patients and controls.

GH deficiency was determined according to the following criteria (17): at least 3 pituitary hormone deficiencies plus 1) IGF-I concentrations lower than mean-3 SD of the control group (<90 ng/ml) and/or 2) maximum stimulated serum GH concentrations lower than 3 ng/ml in response to previously administered L-dopa or glucagon. All patients were GH deficient according to these criteria.

Patients and controls attended the endocrinology clinic of the internal medicine department after an overnight fast of 10-12 h. Patients came at 08:30 h after an overnight fast, without taking the usual morning replacement therapy. The investigation was carried out on outpatient basis. Menstruating women (patients and controls) were studied during the early follicular phase of the menstrual cycle. Anthropometric measurements were taken and venous blood was obtained for measurements of triglyceride, total cholesterol, HDL-cholesterol, routine hematological, liver, renal function tests, free T_4, basal insulin and IGF-I concentrations. After that body composition was determined by bioimpedance analysis and echocardiographic examination was performed.

BMI was calculated as the ratio of weight (kg) divided by height (cm) squared. WHR was calculated as waist circumference (cm measured at the midpoint between the lower costal margin and the iliac crest) divided by hip circumference (cm measured as the greatest circumference around the buttocks).

Systolic and diastolic BP were measured on the right arm of the study subject in an upright sitting position after a at least 5 min rest using a mercury sphygmomanometer. Two readings were recorded for each individual. The average of 2 readings was defined as the subject's BP.

Insulin resistance (IR) was calculated by a computer derived formula (18):

HOMA (homeostasis model assessment) IR=fasting insulin (μU/ml) x fasting glucose(mmol/l)/22.5

Body composition was measured by a bioelectrical impedance analyser (Bodystat 1500, Bodysat Ltd, Douglas, G.B.).

M-mode, two-dimensional and Doppler echocardiographic studies were obtained with a commercially available ultrasound system (GE Vingmed Ultrasound AIS, System Five, Norway) using a 2.5 mHz transducer. M-mode and two-dimensional recordings were made with the subjects in the lateral recumbent position according to the standardization of the American Society of Echocardiography (19). The following indices were assessed and referred to left ventricular end systolic (ESD) and end diastolic diameters (EDD), interventricular septal thickness (IVS), posterior wall thickness (PWT), stroke volume (SV), ejection fraction (EF), fractional shortening (FS=EDD-ESD/EDD%). Calculation of left ventricular mass (LVM) was performed using a previously validated formula (20): mass (g)=0.8 [1.04x (LV internal end-diastolic dimension + IVS + PWT)^3 – (LV internal end-diastolic dimension)^3]+ 0.6. LVM index was calculated by dividing LVM to body surface area.

Table 1 - *Demographic and anthropometric data of the hypopituitary patients and controls.*

	Hypopituitary patients	Controls	*p*
Age (yr)	40.68±13.31	41.15±12.18	NS
Male/female no.	9/10	9/10	NS
BMI (kg/m^2)	26.04±4.66	25.33±4.30	NS
WHR	0.87±0.07	0.84±0.06	NS
Systolic BP (mmHg)	121.05±16.03	122.10±10.71	NS
Diastolic BP (mmHg)	79.21±8.86	76.57±6.02	NS
Heart rate (beats/min)	79.47±7.50	76.26±7.14	NS
Body fat mass* (%)	31.88±10.06	28.88±9.31	NS
Lean body mass* (%)	68.25±10.07	71.48±9.45	NS

NS: not significant; WHR: waist-to-hip ratio; *Determined by bioelectrical impedance analysis. Values are mean±SD. Statistical significance was determined by Student's unpaired *t* test and χ^2 test where appropriate.

Table 2 - *Biochemical and hormonal data of the hypopituitary patients and controls.*

	Hypopituitary patients	Controls	*p*
Glucose (mg/dl)	87.26±10.08	82.42±10.41	NS
Cholesterol (mg/dl)	214.36±52.08	187.10±42.65	NS
Triglyceride (mg/dl)	128.84±53.12	140.05±114.48	NS
HDL cholesterol (mg/dl)	43.89±8.89	41.21±8.31	NS
LDL cholesterol (mg/dl)	144.68±48.61	113.52±30.03	0.02
Insulin (mU/ml)	7.56±6.62	9.79±6.23	NS
HOMAIR	1.65±1.46	2.02±1.32	NS
Free T_4 (pmol/l)	15.32±4.08	16.11±2.15	NS
IGF-I (ng/ml)	66.61±73.97	453.76±121.26	<0.001

HOMAIR: basal insulin (μU/ml) x fasting glucose (mmol/l)/22.5; NS: not significant. Values are mean±SD. Statistical significance was determined by Student's unpaired *t* test.

Indices of left ventricular diastolic filling were derived from pulsed-wave Doppler sampling of transmitral flow: mitral peak early diastolic flow velocity (EPV), mitral peak late diastolic flow velocity (APV), mitral E wave acceleration rate (EACC=velocity time integral from the onset of filling to the peak velocity of the E wave divided by time), mitral E wave deceleration rate (EDEC=velocity-time integral from the peak velocity of the E wave to the cessation of the E wave divided by time), deceleration time (DT=interval between the peak E velocity and the intersection of the deceleration of flow with baseline), mitral A wave acceleration rate (AACC=velocity time integral from the onset of filling to the peak velocity of the A wave divided by time), mitral A wave deceleration rate (ADEC=velocity-time integral from the peak velocity of the A wave to the cessation of the A wave divided by time). Isovolumetric relaxation time (IVRT) was determined by simultaneous recording of the aortic and mitral flowmetry by continuous wave Doppler as the interval between aortic valve closure and the onset of early mitral diastolic flow. For all patients and control subjects peak early/late diastolic mitral flow velocity ratio (EPV/APV) was also calculated. It is previously shown that the EPV/APV ratio normally ranges from 1.0 to 2.0 and ratio <1.0 indicates diastolic dysfunction (14).

All biochemical analyses including glucose, total cholesterol, triglyceride concentrations were performed at the Technicon DAX–72 autoanalyzer (Technicon, Bayer Corporation, U.S.A.) in the Central Biochemistry Laboratory at the Istanbul Faculty of Medicine. HDL cholesterol concentrations were measured at the RA-XT autoanalyzer after phosphotungstic acid and magnesium chloride precipitation. LDL cholesterol was calculated by the Friedewald formula.

Insulin analyses were performed by RIA using a commercially available kit (Diagnostic Systems Laboratories, U.S.A.). Serum free T_4 concentrations were analyzed using ligand analog RIA (Amerlex-M, Amersham International). GH was measured with a conventional RIA kit (Euro-Diagnostica, The Netherlands). Serum IGF-I concentrations were determined by a hydrochloric acid-ethanol extraction RIA (Diagnostic Systems Laboratories, U.S.A.).

Patients and controls were compared using unpaired *t* test. Since triglyceride, insulin and HOMA distributions significantly deviated from a normal distribution, measurements were log-transformed for analysis. However, since the differences in the results were extremely small for between groups comparisons, we presented the results using untransformed means±SD. The correlations between variables were evaluated by simple regression analysis. Significance was taken as $p<0.05$. All analyses were conducted by Statgraphics/PC V 5.0 statistical software (Statistical Graphics Corporation, U.S.A.).

Table 3 - *Left heart dimensions and left ventricular systolic function parameters in hypopituitary patients and controls.*

	Hypopituitary patients	Controls	*p*
Left heart dimensions			
EDD (cm)	4.62±0.50	4.64±0.33	NS
ESD (cm)	2.92±0.50	2.91±0.47	NS
IVS (cm)	0.94±0.13	0.90±0.07	NS
PWT (cm)	0.85±0.19	0.89±0.07	NS
LVM (g)	162.84±52.90	161.68±32.09	NS
LVMI (g/m^2)	93.78±24.19	91.26±12.69	NS
Left ventricular systolic function			
SV (ml)	65.73±13.71	66.52±11.54	NS
EF (%)	66.73±7.14	66.89±9.49	NS
FS (%)	36.68±5.54	37.05±7.66	NS

EDD: end diastolic diameter; EF: ejection fraction; ESD: end systolic diameter; FS: fractional shortening; IVS: interventricular septal thickness; LVM: left ventricular mass; LVMI: left ventricular mass index; PWT: posterior wall thickness; NS: not significant; SV: stroke volume;. Values are mean±SD. Statistical significance was determined by Student's unpaired *t* test.

Table 4 - *Left ventricular diastolic function parameters in hypopituitary patients and controls.*

	Hypopituitary patients	Controls	*p*
EPV (cm/s)	80.94±16.88	88.89±15.46	NS
EACC (cm/s^2)	10.61±4.41	11.43±4.61	NS
EDEC (cm/s^2)	4.80±2.13	5.48±1.68	NS
DT (ms)	247.88±70.65	143.26±31.70	<0.001
APV (cm/s)	69.73±15.32	66.89±12.09	NS
AACC (cm/s^2)	11.62±6.23	10.99±6.38	NS
ADEC (cm/s^2)	5.47±2.62	6.44±2.73	NS
EPV/APV	1.19±0.30	1.37±0.39	NS
IVRT (ms)	122.31±18.24	89.47±12.12	<0.001

AACC: mitral A wave acceleration rate; ADEC: mitral A wave deceleration rate; APV: mitral peak late diastolic flow velocity; DT: deceleration time; EACC: mitral E wave acceleration rate; EDEC: mitral E wave deceleration rate; EPV: mitral peak early diastolic flow velocity; IVRT: isovolumetric relaxation time; NS: not significant. Values are mean±SD. Statistical significance was determined by Student's unpaired *t* test.

RESULTS

The demographic and anthropometric data of the hypopituitary patients and controls are shown in Table 1. No significant differences were observed between hypopituitary patients and controls with respect to age, BMI, WHR, BP, heart rate, percent body fat mass and percent lean body mass.

Serum glucose, total cholesterol, HDL cholesterol and triglyceride concentrations did not change significantly between the patients and controls. Basal insulin and free T_4 concentrations and HOMAIR, a surrogate for insulin resistance, did not either change significantly. However LDL cholesterol concentrations were significantly higher and IGF-I concentrations were significantly lower in the hypopituitary patients than those found in the controls (Table 2).

Table 3 and 4 summarized the echocardiographic parameters in the patients and controls. No significant differences were observed with respect to left heart dimensions and left ventricular systolic function (Table 3). Nevertheless DT and IVRT were significantly prolonged in the hypopituitary patients compared to controls (Table 4, Fig. 1). In addition 5 out of the 19 hypopituitary patients (26%) had EPV/APV ratio lower than 1, indicating diastolic dysfunction. Fourteen of the 19 patients (74%) had IVRT longer than 113 ms (mean+2SD of controls). Fourteen of the 19 patients (74%) had DT longer than 206 ms (mean+2SD of controls). Eleven of the patients (58%) had both an increased IVRT and DT. In the controls, only one of the subjects had IVRT longer than 113 ms (120 ms) and another one subject had EPV/APV ratio lower than 1. None of the subjects had DT longer than 206 ms.

No significant correlation was observed between IVRT or DT and study parameters in the hypopituitary group. No significant correlation was evident between DT and study parameters in the controls either. However IVRT correlated significantly and positively with height (r=0.5787, $p<0.01$), lean body mass percent (r=0.4605, $p<0.05$), E peak velocity (r=0.4827, $p<0.05$) and negatively with fat mass percent (r=-0.5081, $p<0.05$) in the controls.

Significant correlations between IGF-I and study parameters are shown in Table 5. LVM correlated significantly with IGF-I levels in hypopituitary patients and controls. IGF-I was also correlated significantly with some of the parameters of left heart dimensions and systolic function, but no significant correlation was observed between IGF-I and diastolic function parameters. Interestingly, in the control group, correlation coefficient between LVM and

Table 5 - *Significant correlations between IGF-I and study parameters in hypopituitary patients and controls.*

Hypopituitary patients		Controls	
End diastolic dimension	r=0.5025 $p<0.05$	End diastolic dimension	r=0.5433 $p<0.05$
Left ventricular mass	r=0.4620 $p<0.05$	Left ventricular mass	r=0.5595 $p<0.05$
Stroke volume	r=0.5310 $p<0.05$	Left ventricular mass index	r=0.5137 $p<0.05$
		Stroke volume	r=0.5638 $p<0.05$

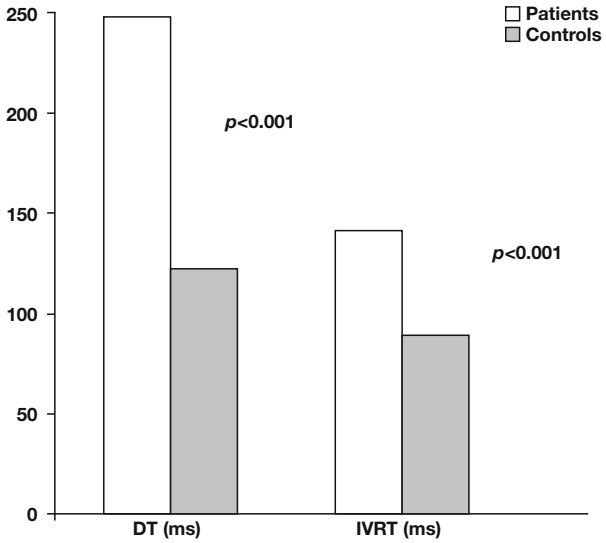

Fig. 1 - *Mean deceleration time (DT) and isovolumetric relaxation time (IVRT) in the hypopituitary patients and controls.*

IGF-I was stronger than that found in the hypopituitary patients.

Body composition was statistically dependent on the duration of hypopituitarism. The time-span of hypopituitarism correlated significantly and positively with percent body fat mass (r=0.6119, $p<0.01$) and negatively with percent lean body mass (r=-0.5949, $p<0.01$) in the hypopituitary patients. But no significant correlation was evident between the echocardiographic indices and the duration of hypopituitarism.

DISCUSSION

Epidemiological evidence indicated an increased incidence of ischemic heart disease and heart failure in hypopituitary patients treated with conventional replacement therapy (21). A causal relationship has been suggested between GH deficiency and increased vascular mortality and morbidity (22). In adults with childhood onset GH deficiency, LVM is decreased and systolic function is impaired (3, 4). These abnormalities are reversed after GH treatment (3, 23, 24). However, in most of the studies, it is pointed out that GH deficiency may not lead to significant changes in LVM and systolic function in adult patients with adulthood onset GH deficiency when compared with controls (7-12). The most likely explanation for the divergences between childhood and adulthood-onset GH deficiencies might be the younger age at onset and longer duration of GH deficiency in childhood disease. It is suggested that congenital GH deficiency has more severe consequences on myocardial growth and development (12). However, in adult patients, even if left ventricular systolic function is normal, subtle abnormalities on diastolic function are evident. Relatively few studies compared diastolic function parameters with controls in adulthood-onset hypopituitary patients.

Johannsson *et al.* (7) found no significant differences between 7 hypopituitary GH deficient men and 21 controls with respect to left heart dimensions, left ventricular systolic and diastolic function indices. But at the end of the GH treatment that lasted 42 months, atrial emptying index was found to be lower than controls, indicating an impairment on left ventricular diastolic function during GH administration. Thuesen *et al.* (9) found no significant differences between patients and controls with respect to E/A ratio. Shahi *et al.* (8) showed that all of the 26 hypopituitary adults treated with conventional replacement therapy had normal LVM index and normal left ventricular ejection fraction. But eight of these 26 patients had abnormal left ventricular diastolic function as measured by prolonged IVRT and decreased E/A ratio. In Shahi's study no matched control group was present and normal values for IVRT and E/A were derived from previous studies of normal subjects. Valcavi *et al.* (12) indicated that left ventricular dimensions, mass and systolic function were normal in 20 patients with adult-onset GH deficiency, but E-wave deceleration time was significantly prolonged. In Valcavi's study no significant differences were observed with respect to IVRT between hypopituitary patients and controls. Beshyah *et al.* (16) reported that in 17 GH deficient patients, IVRT decreased significantly during GH treatment compared with baseline. However in Beshyah's study no comparison was made between hypopituitary patients and healthy controls. Different results in the previously cited studies could be explained by the absence of, in particular body composition, matched healthy controls in most of the studies and diverse indices used to determine diastolic function. Both of DT and IVRT were not studied in the majority of these reports except in the study of Valcavi *et al.* (12). In addition, duration of hypopituitarism and the severity of GH deficiency as determined by the numbers of additional pituitary hormone deficits (25) appeared to be different between study groups. The quoted studies determined cardiac structure and function in GH deficient adults with one or more pituitary hormone deficits other than GH. In addition both childhood and adulthood onset GH de-

ficient patients were included in the study group of Beshyah *et al.* (16). The consequences of GH deficiency range from very mild to severe cardiac dysfunction. This non-uniform pattern could be related to the age at onset, severity and the duration of GH deficiency (26). Therefore, different patient characteristics and non-homogenous study groups may lead to diverse results. In our homogenous patient population consisting of adulthood onset GH deficient patients with at- least 3 pituitary hormone deficits, the duration of hypopituitarism seems not to have an effect on cardiac structure and LVM. Cardiac performance is already significantly impaired when a decrease in LVM is observed, similarly to childhood onset GH deficient patients (3, 4). Therefore our patients may constitute a selected homogenous group to study the subtle effects of GH deficiency on myocardium.

In our study, GH deficient hypopituitary patients had significantly longer IVRT and DT than controls indicating diastolic dysfunction. Diastolic function abnormalities are suggested to precede the deterioration in systolic function (27, 28). DT is a measure of the effective operative chamber compliance of the left ventricle. Prolonged DT indicates an abnormality of relaxation (14). DT may be influenced by changes in passive elastic properties of the left ventricle (29). Prolonged IVRT is an evidence of abnormal left ventricular filling (14). IVRT is reported to be the earliest parameter to be influenced by processes leading to cardiac dysfunction (16). Therefore these abnormalities of diastolic function might be the earliest signs of myocardial dysfunction due to GH deficiency. Our results may also help to explain the increased incidence of cardiac failure in hypopituitary patients (21) when studies indicating that a significant proportion of patients with congestive heart failure have normal systolic function (28, 30) are considered.

Most of the biologic effects of the GH on the heart are known to be mediated by local production of IGF-I (31, 32). In our patients, significant positive correlations were observed between IGF-I and left heart dimension, LVM and stroke volume. IGF-I and GH contribute to improvement in cardiac performance and induction of cardiomyocyte hypertrophy (31-33). In hypopituitary patients, deterioration in left ventricular diastolic function might be explained by the relatively decreased cardiomyocyte mass and increased interstitial connective tissue content. It was previously shown that ultrastructural changes associated with GH deficiency led to a relative decrease in myofibrillar content of cardiomyocytes (5). The decrease in myofibrillar content and relative increase in interstitial connective tissue might increase left ventricular stiffness and might be responsible for the observed diastolic function abnormalities. On the other hand GH treatment can augment myocardial contractility without having an effect on cardiac muscle growth. GH interferes with the $G_i\alpha$-coupled inhibition of phospholipase C activity, leading to decreased $G_i\alpha$ activity (34). This could be a mechanism through which the improvements in contraction are mediated. The early phases of diastole are a complex energy-dependent process during which the contractile elements are deactivated. The IVRT corresponds to the inactivation of actin-myosin cross-links and sarcoplasmic reticulum's energy dependent calcium ion uptake (29). GH deficiency might interfere this energy dependent process through decreased activity of myocardial fibers. To support this suggestion, it was previously shown that GH treatment reversed diastolic function abnormalities without having an effect on LVM in hypopituitary patients although ultrastructural changes in myocardium cannot be excluded (12). In addition, in our patients, prolongation of IVRT was statistically independent of demographic and physiologic confounders that include age, systolic and diastolic BP, body composition, LVM, heart rate and loading condition such as left ventricular diastolic diameter as a rough index of preload. The lack of correlation between IVRT and LVM, left ventricular diastolic diameter or diastolic BP (a type of contraction load) in our hypopituitary patients suggests that inactivation-dependent impairment of relaxation might predominate. Endomyocardial biopsy samples for histological and electron microscope studies could have been used to examine the changes in myofibrillar content in particular patients with dilated cardiomyopathy due to long-term GH deficiency. Alternatively measurements of calcium handling by cardiomyocytes could be used to understand the effects of GH deficiency on active diastole.

In our study significant positive correlations were observed between myocardial mass and IGF-I levels in the patients and controls. These findings may indicate that even in healthy adults, IGF-I levels still have an effect on the maintenance of myocardial mass.

Duration of hypopituitarism has an adverse effect on body composition in our study. No effect was evident for the echocardiographic left heart indices. This finding supports the suggestion that more time is needed to reveal the significant detrimental effects of GH deficiency on myocardial mass and

function like those observed in childhood onset GH deficiency.

In summary, it is concluded that in adult patients with adulthood onset GH deficiency, left ventricular diastolic function at rest is impaired. This finding might indicate the preclinical stage of a specific cardiomyopathy due to GH deficiency. Further studies are needed to determine the pathophysiological mechanisms responsible for diastolic dysfunction in patients with GH deficiency.

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