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ORIGINAL ARTICLE

Left ventricular functions in children with newly diagnosed Graves' disease. A single-center study from Upper Egypt

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Abstract This study aimed to evaluate the left ventricular (LV) functions in a cohort of children with Graves' disease (GD). This is a cross-sectional case-control study. It included 36 children with GD and 36 healthy children matched for age and gender. Thyroid hormones (TSH, FT4, and FT3) and anti-thyroid autoantibodies [anti-thyroid peroxidase (anti-TPO), thyrotropin receptor (TRAbs), and thyroglobulin antibodies] were measured. Conventional and tissue Doppler imaging (TDI) echocardiographies were used to assess left ventricular systolic and diastolic functions. LV mass index (LVMI) and myocardial performance index (MPI) were also measured. Compared to healthy children, conventional echocardiography of patients with GD revealed higher LVMI (P = 0.001) indicating LV hypertrophy but normal LV functions while TDI revealed lower Em/Am ratio indicating LV diastolic dysfunction (P = 0.001). Significant correlations were reported between FT4 with LVMI (P = 0.05), Em/Am (P = 0.01), and MPI (P = 0.01). In multivariate analysis, a positive correlation was identified between FT4 with MPI (OR = 1.17; 95% CI = 1.09–1.15; P = 0.001).

Conclusions: Children with newly diagnosed GD may have significant subclinical changes in LV structure and function (diastolic and global). TDI is more sensitive than conventional Doppler in detecting LV dysfunction. These findings highlight the importance of early monitoring of children with GD for left ventricular mass index and diastolic function.

What is Known:
- *There is an increased risk for cardiac abnormalities in children with Graves' disease (GD).*
- *Limited studies assessed left ventricular function in patients with GD.*

What is New:
- *Children with newly diagnosed GD may have significant subclinical changes in left ventricular structure and functions.*
- *Children with newly diagnosed GD should be monitored for left ventricular mass index and diastolic function.*

Keywords Graves' disease · Tissue Doppler imaging · Echocardiography · Left ventricular function · Left ventricular mass index · Diastolic function · Myocardial performance index

Abbreviations

BMI	Body mass index
GD	Grave's disease
LVMI	Left ventricular mass index
MPI	Myocardial performance index
TDI	Tissue Doppler imaging

Introduction

Graves' disease (GD) is the most common cause of hyperthyroidism in pediatric population accounting for 10–15% of

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thyroid diseases in children younger than 18 years [32]. GD results from a complex interaction between genetics, environment, and immune system. The immune system produces autoantibodies, thyroid-stimulating hormone receptor antibodies (TRAbs), which stimulate the thyroid gland to produce excess thyroid hormones [4]. The overproduction of thyroid hormones results in structural and functional cardiac changes with higher rates of morbidity and mortality [18]. The cardiovascular complications of GD are believed to be the results of direct effect of excess thyroid hormones on cardiac tissue and their indirect effects on the sympathetic nervous system, peripheral vascular smooth muscle, renin–angiotensin–aldosterone system, erythropoietin production [11], and regulation of expression of some structural and regulatory genes [19]. In recent years, there are few studies which evaluated cardiac functions in adults with GD. However, the available results are contradictory [3, 16, 21]. To our knowledge, there is no published data about left ventricular function in children with GD. This study aimed to evaluate the left ventricular (LV) functions in a cohort of children with newly diagnosed GD using conventional and tissue Doppler imaging echocardiographies.

Patients and methods

Patients

This is a cross-sectional case-control study. It included 36 children and adolescents (girls = 29; boys = 7) with a diagnosis of GD. All were newly diagnosed. Their age range was 9–18 years (mean age = 14.4 ± 2.6 years). Patients were recruited consecutively from the Pediatric Endocrinology Clinic of Assiut Children University Hospital, Assiut, Egypt. Diagnosis of GD was based on the presence of clinical manifestations of hyperthyroidism, low serum level of thyroid-stimulating hormone (TSH), high serum levels of free thyroxine (FT4), free triiodothyronine (FT3), and high titers of anti-thyroid autoantibodies which included anti-thyroid peroxidase antibodies (anti-TPO antibodies or TPOAbs) and/or thyrotropin receptor antibodies (TRAbs) and thyroglobulin antibodies (TgAbs) [31]. This study also included 36 healthy children, matched for gender (girls = 30; boys = 6), age (range = 9–18 years; mean age = 15.6 ± 3.4 years), pubertal status, and socioeconomic status, recruited from the general population. Excluded from the study were children with other medical, systemic or autoimmune disease, toxic adenoma or toxic multinodular goiter, and subclinical hyperthyroidism and those who used drugs which may influence the cardiovascular parameters.

The study protocol was performed in accordance with the standards laid down in the Declaration of Helsinki and its later amendments and approved by the Ethics Committee of Faculty of Medicine, Assiut University, Assiut, Egypt. Informed written consents were obtained from the parents of all participants before enrollment in the study.

Methods

All participants underwent the following: (1) clinical medical workups including histories and physical examinations, (2) thyroid ultrasonography, (3) a standard 12-lead electrocardiogram (ECG), (4) measurement of blood pressure in the supine and upright position (Dinamap automated vital sign monitor; Criticon, Germany), and (5) calculation of body mass index (BMI). Height and weight were measured using a wall-mounted stadiometer and a calibrated weight scale and the child was wearing the underwear only. BMI was calculated using the following formula: BMI = weight (kg)/height $(m)^2$. BMI was expressed as standard deviation scores (SDSs) using the Egyptian Growth Reference Data [10]. Puberty was assessed using the standardized method of Tanner stages [22].

Laboratory investigations

For all participants, after an overnight fast, at 8.00 a.m., blood was withdrawn for the estimation of the serum levels of TSH, FT4, and FT3 using ultrasensitive immunometric assays (Immulite™ 2000 Third Generation, Diagnostic Products Corporation, Los Angeles, CA). The reference ranges for thyroid hormones were as follows: TSH = 0.4–4.0 mU/L, FT4 = 10.0–26.0 pmol/L, and FT3 = 3.5–5.5 pmol/L. The coefficients of variations (CV) for thyroid hormones were as follows: TSH = 5.0 and 5.1% at concentrations of 4.0 and 10.0 mU/L, respectively; FT4 = 6.5% at concentrations of 10.0 pmol/L; and FT3 = 8.9% at concentrations of 3.5 pmol/L. The serum TPOAbs and TgAbs levels were measured by rapid enzyme-linked immunosorbent assay (ELISA) (Genesis Diagnostics, Little port, UK). TgAb and TPOAbs concentrations more than 100 and 75 IU/mL, respectively, were considered positive. The serum TRAbs level was measured with the 3rd generation TBII assay (TRAb3rd) using the automated Cobas electrochemiluminescence (Elecsys, Roche Diagnostics GmbH, Penzberg, Germany). The cut-off value for positive concentration of TRAbs was 1.75 IU/L.

Conventional echocardiography

Echocardiography with simultaneous ECG (standard lead II) was performed for patients and controls using a S4-2 broadband sector (4- to 2-MHz phased-array transducer; Philips EnVisor C HD ultrasound system; Philips Medical Systems, Inc., Netherlands). M-mode measurements and conventional Doppler echocardiographic examinations were performed according to the criteria of the American Society of Echocardiography (ASE) guidelines [29]. M-mode echocardiography was obtained on the left sternal border. The following

parameters were measured: LV dimension, LV fractional shortening (FS), LV ejection fraction (EF) [26], LV mass (LVM), and LV mass index (LVMI) [9]. LV diastolic function was evaluated by mitral inflow velocities obtained in the apical four-chamber view. The following parameters were measured: early peak flow velocity (E), atrial filling velocity (A), E/A ratio, early filling deceleration time (DcT), and isovolumic relaxation time (IVRT) [26]. All measurements were recorded as an average of three cardiac cycles. Myocardial performance index (MPI) was obtained in the apical five-chamber view using the following formula [30]: MPI = IVCT + IRT/ET. The isovolumetric contraction time (IVCT) is the interval between the end of mitral flow and the beginning of aortic flow. The IVRT is the interval between the end of aortic flow and the beginning of the following mitral flow. The ejection time (ET) is the interval from the beginning of aortic flow until the end.

Tissue Doppler imaging

Pulsed-wave Doppler imaging was used to record the longitudinal myocardial velocities. The sample volume was placed at the ventricular myocardium immediately adjacent to the mitral annulus. The following TDI parameters were evaluated: peak systolic (Sm), peak early diastolic (Em), peak late diastolic (Am) myocardial velocities, and Em/Am. For each parameter, three cardiac cycles were averaged. Pediatric references for TDI variables were used for comparisons [7]. For each child, echocardiographic examinations were done by two expert pediatric cardiologists who were unaware of the clinical diagnosis of the studied cases.

Statistical analysis

Calculations were done with the statistical package SPSS for windows, version 16.0 (SPSS Inc., Chicago, IL, USA). Quantitative data were expressed as mean ± SD. Student's *t* test was used to compare between means. Pearson's correlation coefficient was used to look for association between values of TSH, FT4, and TRAbs with the echocardiographic parameters. Multivariate analysis was used to detect the significant associations between laboratory and echocardiographic parameters. For all tests, values of $P \leq 0.05$ were considered statistically significant.

Results

This study included 36 children with GD. Compared to healthy children, patients had significantly lower BMI SDS ($P = 0.01$) and higher heart rate ($P = 0.01$). Table 1 showed the demographic, clinical, and laboratory characteristics of the studied groups. Tables 2 and 3 showed the conventional and tissue Doppler echocardiographic findings of the studied groups. Compared to healthy children, patients had significantly higher LVMI ($P = 0.01$), IVRT ($P = 0.001$), and LV MPI ($P = 0.001$) and lower Em ($P = 0.01$) and Em/Am ratio ($P = 0.01$). The Am value was higher in patients compared to healthy children but did not reach a statistical significance value. The LV systolic function was preserved in patients as evidenced by the normal peak systolic velocity (Sm). In patients with GD, significant correlations were observed between LVMI with TSH ($P = 0.05$) and FT4 ($P = 0.05$); between Em/Am ratio with FT4 ($P = 0.01$); and between MPI with TSH ($P = 0.05$), FT4 ($P = 0.01$), and TRAbs ($P = 0.05$) (Table 4). In multivariate analysis, significant correlation was observed between FT4 with MPI (OR = 1.17; 95% CI = 1.09–1.15; $P = 0.001$).

Discussion

Previous studies in adults with overt hyperthyroidism revealed higher LVMI [6, 14]. In accordance, this study indicates that children with GD had higher LVMI which also significantly correlated with the serum levels of FT4 and TRAbs. In contrast, Biondi et al. [2] did not find a significant correlation between hormonal status and LVM in adults with hyperthyroidism. The differences in the results between different studies could be attributed to the use of heterogeneous group of patients and the differences in duration of exposure to excess thyroid hormones. The exact mechanism of ventricular hypertrophy in association with GD is unknown but seems to be multiple. It has been suggested that excess thyroid hormones and the chronic hemodynamic overload (due to primary hyperthyroidism [12] or secondary to the effect of anti-thyroid receptor autoantibodies [5, 8]) stimulate the expression of cardiac contractile protein synthesis in cardiac myocardial myocytes resulting in cardiac hypertrophy [6]. This is supported by the finding of cardiac hypertrophy in patients receiving thyroxine in the absence of significant changes in heart rate and blood pressure, suggesting that there is a direct trophic effect of thyroid hormone on the myocardium [13].

In this study, we did not identify evidence of impairment of LV systolic function with either conventional or TDI. In adults, studies of the effect of GD on LV systolic function are controversial. Some did not report LV systolic dysfunction in adults with GD [17, 23], while few reported increased contractility and left ventricular ejection fraction (LVEF) in adults with GD [17, 28]. Also, impaired reversibility of LVEF was reported in patients with thyrotoxic cardiomyopathy [25]. In this study, although normal LV diastolic function (as evidenced by normal E/A ratio, IVRT, and mitral DcT) was reported using conventional Doppler echocardiography, however, lower Em/Am ratio was reported using TDI. The presence of a negative correlation between Em/Am ratio and FT4

Table 1 Demographic, clinical, and laboratory characteristics of the studied groups

Characteristics	Patients (n = 36)	Controls (n = 36)	P value
Age; years	14.4 ± 2.6	15.6 ± 3.4	0.244
Female/male	29/7	30/6	0.462
BMI SDS	− 0.38 ± 1.05	0.3 ± 2.14	0.01
Heart rate; beats per minute	112.5 ± 12.5	88.6 ± 9.3	0.01
Systolic blood pressure; mmHg	110.3 ± 14.4	108.5 ± 10.2	0.136
Diastolic blood pressure; mmHg	75.4 ± 6.2	73.6 ± 8.6	0.452
TSH; mIU/mL	0.0561 ± 0.5	1.95 ± 0.9	0.001
FT4; pmol/L	33.9 ± 11	12.2 ± 2.8	0.001
FT3; pmol/L	11.5 ± 5.4	4.3 ± 2.2	0.001
TPOAbs; IU/mL	348.7 ± 43.9	16.7 ± 4.5	0.001
TRAbs; IU/L	18.8 ± 3.2	0.6 ± 0.3	0.01
TgAbs; IU/mL	199.4 ± 23.8	28.1 ± 14.6	0.001

Data are expressed as means ± standard deviation (SD)

BMI-SDS body mass index slandered deviation score; *TSH* thyroid-stimulating hormone; *FT4* free thyroxine; *FT3* free triiodothyronine; *TPOAbs* thyroid peroxidase antibodies; *TRAbs* thyrotropin-stimulating hormone receptor antibodies; *TgAbs* thyroglobulin antibodies

suggests that excess of thyroid hormone may impair LV diastolic function. The exact mechanism of LV dysfunction in association with GD is unknown. We suggest that chronic hemodynamic overload and the increase in LVMI may impair myocardial relaxation resulting in diastolic dysfunction.

In this study, children with GD had higher MPI despite normal systolic function. In addition, in multivariate analysis, a positive correlation was identified between FT4 levels and MPI, suggesting that FT4 has a role in global LV dysfunction in children with GD [15]. MPI is considered as an easy-performed and recordable parameter and a useful clinical index of global ventricular function (systolic and diastolic functions). It is also particularly useful as a predictor of clinical outcome [24, 30].

To summarize, the results of this study indicate that (1) newly diagnosed children with GD may have LV hypertrophy and (2) TDI is more sensitive in detecting early diastolic dysfunction in children with GD compared to conventional echocardiography. The presence of diastolic dysfunction in an asymptomatic patient is a risk factor for the future development of heart failure; thus, early identification may provide a rationale for preventive and therapeutic strategies [1, 27] (for example, the early use of anti-thyroid drugs, beta-blockers, and calcium channel blockers can reverse ventricular remodeling [20]).

Table 2 Conventional echocardiographic findings of the studied groups

Parameters	Patients (n = 36)	Controls (n = 36)	P value
LVEDD; mm	51.6 ± 8.4	47.6 ± 5.3	0.324
LVESD; mm	25.8 ± 7.2	24.5 ± 6.5	0.660
FS%	50.9 ± 4.5	46.2 ± 5.3	0.312
EF%	71.4 ± 5.2	70.2 ± 4.6	0.725
LVMI; g/m^2	84.5 ± 25.6	63.7 ± 18.9	0.01
IVSWT; mm	7.5 ± 2.2	6.8 ± 3.2	0.730
LVPWT; mm	6.7 ± 2.1	5.6 ± 1.4	0.972
E/A ratio	1.17 ± 0.10	1.34 ± 0.22	0.524
Mitral DcT; ms	188.5 ± 16.2	169.4 ± 15.3	0.083
IVCT; ms	47.3 ± 8.3	50.4 ± 17.6	0.294
IVRT; ms	87.7 ± 8.5	43.3 ± 22.8	0.001
ET; ms	245.5 ± 19.0	252.7 ± 34.0	0.05
MPI	0.55 ± 0.10	0.37 ± 0.15	0.001

Data are expressed as mean ± standard deviation (SD)

LVEDD left ventricular end-diastolic diameter; *LVESD* left ventricular end-systolic diameter; *FS* fractional shortening; *EF* ejection fraction; *LVMI* left ventricular mass index; *IVSWT* interventricular septal wall thickness; *LVPWT* left ventricular posterior wall thickness; *E/A* ratio, mitral E- to mitral A-wave peak velocity; *IVCT* isovolumic contraction time; *IVRT* isovolumic relaxation time; *DcT* deceleration time; *ET* ejection time; *MPI* myocardial performance index

Limitations of the study

Despite the significance of the data of this study, it has some limitations. The small sample size is the main limitation of the

Table 3 Tissue Doppler imaging indices of the studied groups

Parameters	Patients (n = 36)	Controls (n = 36)	P value
Peak Em	0.15 ± 0.01	0.13 ± 0.02	0.01
Peak Am	0.05 ± 0.01	0.06 ± 0.01	0.273
Em/Am	2.3 ± 0.02	2.9 ± 0.01	0.01
Peak Sm	0.67 ± 0.02	0.68 ± 0.01	0.525

Data are expressed as means ± standard deviation (SD)

Em peak early; *Am* peak late; *Sm* peak systolic myocardial velocity

Table 4 Correlations between FT4, TSH, and TRAbs with echocardiographic parameters of the studied patients

Echocardiographic parameters	FT4 (*r* and *P* values)	TSH (*r* and *P* values)	TRAbs (*r* and *P* values)
LVEDD; mm	0. 198	0.211	0.221
LVESD; mm	0.204	0.165	0.198
FS%	0.258	0.228	0.235
EF%	0.212	0.188	0.234
LVMI; g/m^2	+ 0.447*	− 0.301*	0.321
E/A ratio	0.199	0.205	0.185
IVRT; ms	0.235	0.186	0. 154
DcT; ms	0.222	0.209	0.217
Em/Am ratio	− 0.432**	0.175	− 0. 211
MPI	+ 0.472**	− 0.341*	+ 0.328*

LVEDD left ventricular end-diastolic diameter; *LVESD* left ventricular end-systolic diameter; *FS* fractional shortening; *EF* ejection fraction; *LVMI* left ventricular mass index; *E/A* ratio, mitral E- to mitral A-wave peak velocity; *IVRT* isovolumic relaxation time; *DcT* deceleration time; *MPI* myocardial performance index

*Significance <0.05

**Significance 0.01

study as this decreases the power of the multivariate analysis. The lack of temporal relationship between LV hypertrophy, LV dysfunction, and severity of clinical manifestations of GD is another limitation. Further, longitudinal studies on a large sample size have to be designed to also determine the changes in cardiac function after treatment and correction of the hyperthyroid status.

Conclusions

Children with newly diagnosed GD may have significant subclinical changes in LV structure and function (diastolic and global). TDI is more sensitive than conventional Doppler in detecting LV dysfunction. These findings highlight the importance of early monitoring of children with GD for left ventricular mass index and diastolic function.

Authors' contributions KA participated in the design of the protocol of the study, coordination of the research, performance of the clinical part, analyses of the data, and writing the draft of the paper. HS participated in the design of the protocol of the study, performed the echocardiography, and participated in the analyses of the data and writing the draft of the paper. AA performed the laboratory investigations and participated in the analyses of the results. All the authors read and approved the manuscript.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

Ethical approval The study protocol was approved by the Ethics Committee of Faculty of Medicine, Assiut Children University Hospital, Assiut, Egypt.

Informed consent Written informed consents were obtained from the parents of all participants.

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