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Original Article

Paediatrics Section

Echocardiography in Transfusion Dependent Beta Thalassaemia Major Egyptian Children: Correlation with Thyroid Function Status and Ferritin Level

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ABSTRACT

Introduction: Iron-mediated cardiomyopathy is leading cause of death in β-thalassaemia (βTM). Thyroid dysfunction maybe associated with cardiac dysfunctions. Early detection of cardiac-function impairment can help in preventing further cardiac damage by modifying disease progression and treatment.

Aim: To assess cardiac function and echocardiography indices in transfusion dependent βTM children in Qena, Egypt and correlate findings with thyroid status and serum ferritin levels.

Materials and Methods: This was a case-control study conducted on 40 transfusion dependent βTM cases aged from 6-12 years who were on regular follow-up in outpatient paediatric clinic in Qena university hospital between January 2016 and December 2016. Fifteen, age and sex-matched healthy children were included as a control group to investigate Left Ventricle (LV) diastolic and systolic function using echocardiography, and correlate findings with serum Thyroid Stimulating Hormone (TSH), free thyroxine (FT4), and serum ferritin. SPSS version 22 used for data analysis and Pearson correlation was used to explore the relationship between quantitative variables. All statistical tests were two tailed, and a p-value below 0.05 was considered statistically significant.

Results: In children with βTM had a mean age 9.51 years (SD±3.26), (n=10, 25%) had hypothyroidism; primary (n=1, 2.5%), subclinical (n=5, 12.5%) and central (n=4, 10%). Cases had Left Ventricular Ejection Fraction percentage (LVEF%) of 67.68±7.04, ferritin level of 2617±1866 vs. 118±43 in control; (p-value=<0.001), Left Ventricular Dimensions at the End of Systole (LVESD) 40.63±6.17 vs. 36.53±4.82 in control; (p-value=0.025) and Left Ventricular Dimensions at the End of Diastole (LVEDD) was 25.40±4.83 vs. 22.60±3.54 in control; (p-value=0.046). Cases with impaired thyroid function had higher ferritin and lower EF%. Cases displayed left ventricular diastolic restrictive pattern with preserved left ventricular systolic function in echocardiogram. FT4 showed a negative correlation with TSH and myocardial performance index (LV Tei) while ferritin showed a positive correlation with TSH, LVEDD and LVESD.

Conclusion: Periodic evaluation of thyroid and cardiac functions and thyroxine replacement maybe considered in cases with iron overload, subclinical hypothyroidism and poor response to chelation therapy.

Keywords: Beta-thalassaemia major, Diastolic function, Echocardiography, Ferritin, Tei index, Thyroid hormone

INTRODUCTION

β-Thalassaemia (βTM) is the most common chronic haemolytic anaemia in Egypt [1]; as a consequence of reduced or absent synthesis of beta globin chains, there is an in imbalance of globin chains causing haemolysis and impaired erythropoiesis leading to affected children to acquire lifelong blood transfusions [2]. However, multiple blood transfusions can lead to iron overload resulting in endocrine dysfunction that might disturb single or multiple endocrine glands [3].

Management strategies have improved the survival and complication-free survival in βTM. However, many transfusion-dependent patients continue to develop iron-induced cardiomyopathy which is responsible for tissue damage and finally death [4]. Myocardial siderosis was observed in nearly one-third of βTM patients [5]. Iron toxicity may indirectly affect heart function by damaging other organs in varying degree as thyroid gland causing hypothyroidism [6]. Hypothyroidism can lead to bradycardia, decreased LV function, pericardial effusion, and increased peripheral vascular resistance [7].

Thyroid dysfunction is frequently present in βTM, but its prevalence and severity varies in different cohorts, and its long-term natural history is poorly understood [8]. Hypothyroidism includes primary hypothyroidism, subclinical hypothyroidism, as well as secondary (central) hypothyroidism.

In a study of Gharzuddine WS and his coworkers, for LV function in βTM patients, LV by Echocardiogram (echo), reported variable abnormalities depending on the patient's age and disease severity [9]. Early detection of cardiac-function impairment can help in preventing further cardiac damage by modifying disease progression and treatment.

We aimed to assess cardiac function in transfusion dependent βTM children in Qena, Egypt, using conventional echocardiogram and correlate findings with thyroid hormones {free thyroxine (FT4) and Thyroid Stimulating Hormone (TSH)} and serum ferritin levels.

MATERIALS AND METHODS

This was a cross-sectional study conducted between January 2016 and December 2016. The study involved 40 transfusion-dependent βTM cases aged from 6-12 years who were on regular follow up in the outpatient clinic. Sample size was calculated at power 80%, to be at least 36. In addition, apparently 15 healthy age and sex-matched children with no hepatic or renal disease, had normal echocardiogram, and negative blood tests for thalassaemia were considered for the control group. They were included from the outpatient clinic of Paediatric Department, Qena University Hospital. A written informed consent was obtained from the parents of each child. The study was approved by the ethics and Research committee of Qena faculty of medicine and in accordance with Declaration of Helsinki.

Children diagnosed with βTM major, were included in the study aged from 1 to 15 years. Diagnosis of βTM was based on clinical presentation, family history, haematological indices and haemoglobin electrophoresis.

All of the included cases were subjected to full medical history evaluation and complete clinical examination, including age, sex, weight, height, disease duration, first time of blood transfusion, number of blood transfusions/year, history of splenectomy, type and duration of chelation therapy. All cases were on regular blood transfusion with 10-15 mL/kg packed cells every 21-25 days, and iron chelation therapy with subcutaneous desferrioxamine (40 mg/kg/day administered through a battery-operated portable pump over a period of 8-12 hours overnight, for 5-7 nights/week).

According to mean pretransfusional haemoglobin level, βTM major cases were subdivided into adequately transfused group (with mean pretransfusional haemoglobin ≥9 g/dL) and inadequately transfused group (with mean pretransfusional haemoglobin <9 g/dL).

According to the mean serum ferritin level, βTM major cases were subdivided into well-chelated group (with mean serum ferritin <2500 ng/mL) and poorly chelated group (with mean serum ferritin ≥2500 ng/mL).

Patients with βTM minor and intermedia and those with acute illness, any hormonal therapy or severe liver disease or end-stage renal disease with creatinine clearance <30% of normal or advanced heart failure or hypertensive cardiomyopathy; subjects with a family history of thyroid dysfunction, genetic, metabolic or neurodegenerative disease or with other medical illnesses have known to impact the primary organ systems of interest were also excluded; e.g., congenital heart defects.

Both cases and controls were subjected to detailed history taking and thorough clinical examination with special emphasis on growth parameters according to the Egyptian growth curves and signs of hypothyroidism, and were subjected to:

Blood sampling: Five mL blood was drawn from each patient and control and divided into: 2 mL on Ethylene Di-Amine Tetra-Acetic acid (EDTA) tube for blood count using Cell dyne 1800 cell counter (Abbott diagnostics, USA), reticulocyte count and haemoglobin electrophoresis (using automated cation-exchange High-Performance Liquid Chromatography (HPLC) D-10 provided by Bio-Rad Laboratories (Bio-Rad Laboratories, USA). 3 mL blood put in plain tube allowed to clot and then centrifuged for 10 minutes at 3,000 rpm and serum is separated for the analysis of serum ferritin, TSH and FT4 using automated Chemiluminescent Microparticle Immune Assay (CMIA) utilizing ChemiFlex Technology (Architect i2000, Abbott diagnostics, USA). Reference range was 0.43-3.28 mU/L for TSH and for FT4 10.80-16.80 pmol/L. Diagnosis of thyroid dysfunction was based on the following criteria; Primary hypothyroidism when FT4 is <12 pmol/L and TSH is >4 mIU/mL; subclinical hypothyroidism when FT4 is normal and TSH is >4 mIU/mL; central (secondary) hypothyroidism when FT4 is <12 pmol/L and TSH is low or normal.

Conventional two-dimensional (2D) Doppler echocardiography: (Vivid S5, Germany, syncmaster 450 MB) with a 2.0-3.5 MHz transducer; utilizing pulsed Doppler, M mode and continuous Doppler on TR jet was used to assess the following echo parameters as implemented by [10]:

- **Dimensions of systolic function:** the LVESD and diastole (LVEDD), EF% was measured using Teichholz formula and fractional shortening (FS%).
- **Evaluation of diastolic function:** The LV diastolic filling indices include early diastolic wave (E-wave), late diastolic wave (A-wave), E-wave to A-wave (E/A) ratio.
- **The myocardial performance index:** the Tei index, is a combined index of systolic and Tei LV i.e., the sum of Isovolumetric Contraction Time (IVCT) and Isovolumetric Relaxation Time (IVRT) divided by the Ejection Time (ET) and was used for quantification of global LV function. Tei LV index is considered abnormal when exceeds 0.30.
- **Pulmonary artery pressure:** using the TR jet (where pulmonary artery systolic pressure was calculated from the pressure gradient through the tricuspid valve using the Bernoulli equation and by adding the right atrial pressure to the pressure gradient of TR jet; pulmonary hypertension was considered when it exceeds 36 mmHg.

STATISTICAL ANALYSIS

Analysis of data was done using SPSS version 22 (IBM SPSS statistics; USA) as follows: description of quantitative variables as Mean±Standard Deviation (SD) and range compared by independent t-test. Description of qualitative variables as number and percentage and will be compared by chi-square test. Pearson's correlation coefficient was used to explore the relationship between quantitative variables. All statistical tests were two tailed, and a p-value below 0.05 was considered statistically significant.

β-TM cases Personal characteristics and clinical parameter		n (%)
Age	<9 years ≥9 years	17 (42.5) 23 (57.5)
Sex	Male Female	29 (72.5) 11 (27.5)
Consanguinity	Positive Negative	31 (77.5) 9 (22.5)
Family History of Similar Condition	Positive Negative	29 (72.5) 11 (27.5)
Associated other chronic haemolytic anaemia	Yes No	1 (2.5) 39 (97.5)
Duration of blood transfusion therapy (years)	<6 years ≥6 years	13 (32.5) 27 (67.5)
Blood transfusion Frequency	Not frequent Frequent/2weeks	33 (82.5) 7 (17.5)
Iron chelating agents	Irregular Regular	20 (50) 20 (50)
Splenomegaly	Positive Negative	34 (85) 6 (15)
Splenectomy	Done Not done	15 (37.5) 25 (62.5)
Hepatomegaly	Positive Negative	16 (40) 24 (60)
Signs of heart failure	Yes No	0 40 (100)
Signs of arrhythmia	Yes No	0 40 (100)
Signs of hypothyroidism	Yes No	0 40 (100)
HB (g/dL)	<10 >10	39 (97.5) 1 (2.5)
S. ferritin (μg/dL)	<2500 ≥2500	16 (40) 24 (60)
TSH (μIU/mL)	Normal High	34 (85) 6 (15)
FT4 (pmol/L)	Normal Low	36 (87.5) 5 (12.5)

[Table/Fig-1]: Clinical and laboratory data of studied cases.
Hb: Haemoglobin; TSH: Thyroid simulating hormone; FT4: Free thyroxin

RESULTS

A total of 40 βTM patients 29 were males (72.5%) and 11 females (27.5%) and 15 healthy subjects as control were enrolled in the study, male (n=13, 86.7%) and female (n=2, 13.3%). None of the patients had signs and symptoms of heart failure, arrhythmia and thyroid disease and 55% were poorly chelated, summary of clinical and laboratory data [Table/Fig-1].

Total number of cases with impaired thyroid function was (n=10, 25%); serum ferritin value was significantly higher in all the four groups of thalassaemia patients [Table/Fig-2].

Pattern of thyroid function in β-TM cases		n (%)	Ferritin (ug/dL)
High TSH+Low FT4	Primary hypothyroidism	1 (2.5%)	6639
High TSH+Normal FT4	Subclinical hypothyroidism	5 (12.5%)	4065.6±2745
Normal TSH+Low FT4	Central hypothyroidism	4 (10%)	2609.9±2364
Normal TSH+Normal FT4	Euthyroid	30 (75%)	2242.7±1414

[Table/Fig-2]: Pattern of thyroid hormones in relation to serum ferritin levels in βTM cases.
TSH: Thyroid simulating hormone; FT4: Free thyroxin

Parameter (Mean±SD)		Groups		t-test	
		βTM cases	Control	t	p-value
Age (years)	Mean±SD	9.51±3.26	8.73±2.55	0.833	0.409
Weight (kg)	Mean±SD	23.20±6.29	24.07±8.71	0.534	0.596
Height (cm)	Mean±SD	120.10±14.08	123.47±15.40	0.602	0.549
HC (cm)	Mean±SD	51.56±1.92	51.27±2.49	0.469	0.641
Heart rate (bpm/minute)	Mean±SD	100.57±9.77	94.9±6.45	2.066	0.044*
	Range	80-124	85-110		
Systolic BP (mmHg)	Mean±SD	95.50±9.86	104.00±10.56	2.794	0.007*
	Range	80.0-120.0	90.0-120.0		
Diastolic BP(mmHg)	Mean±SD	66.25±8.07	71.33±5.16	2.266	0.028*
	Range	50.0-80.0	60.0-80.0		
TSH (mIU/mL)	Mean±SD	2.89±0.89	2.79±1.34	0.279	0.781
	Range	1.0-7.5	1.4 - 4.5		
Free T4 (pmol/L)	Mean±SD	17.28±4.03	16.17±3.19	1.104	0.275
	Range	7.08-23.04	12.0-23.17		
Hb(g/dL)	Mean±SD	7.65±0.90	12.27±0.65	18.106	<0.001**
	Range	5.0-11.1	11.0-13.0		
S. ferritin (ug/dL)	Mean±SD	2617.2±1865.9	118.3±42.5	5.156	<0.001**
	Range	309.0-7505.0	65.0-210.0		
Dimensions of systolic function	LVEDD (mm/M^2)	40.63±6.17	36.53±4.82	2.313	0.025*
	LVESD (mm/M^2)	25.40±4.83	22.60±3.54	2.044	0.046*
	LVEF %	67.68±7.04	67.93±7.17	-0.121	0.904
	FS%	38.05±5.70	37.53±5.88	0.297	0.768
Dimensions of diastolic function	E wave (cm/sec)	114.78±20.16	97.67±14.67	2.995	0.004*
	A wave (cm/sec)	57.05±18.91	53.20±13.85	0.718	0.476
	E/A ratio	2.20±0.69	1.91±0.43	1.538	0.130
(Tei LV)		0.29±0.32	0.34±0.14	-0.555	0.581
Pulmonary artery systolic pressure		37.79±9.21	32.80±6.34	1.928	0.059

[Table/Fig-3]: Demographic data, clinical, laboratory data and echo parameters in βTM patients and controls.
*significant; Head circumference: HC TSH: Thyroid simulating hormone; FT4: Free thyroxin; LVEDD: Left ventricle end diastolic diameter; LVESD: Left ventricle end systolic diameter; LVEF: Left ventricular ejection fraction; FS: Fractional shortening; E wave: Early diastolic flow velocity; A wave: Late diastolic flow velocity

βTM cases had significantly higher heart rate (p-value=0.044) and ferritin level (p-value=<0.001), significant lower systolic BP (p-value=0.007), diastolic BP (p-value=0.028), Hb level (p-value=<0.001), significant larger dimensions of LVEDD (p-value=0.025), LVESD (p-value=0.046) and E-wave value (p-value=0.004) [Table/Fig-3].

Parameter (Mean ± SD)		Thyroid function in cases		Control	p-value
		Impaired	Euthyroid		
Age (years)		10.5±3.14	9.18±3.29	8.82±2.68	0.1349[a] 0.6451[b] 0.2747[c]
Transfusion therapy duration (years)		9.35±3.06	7.53±3.55	-	0.1558
Hb (g/dL)		7.88±0.42	7.57±1.01	12.14±0.67	<0.00001[a] <0.00001[b] 0.3481[c]
Ferritin (ug/dL)		4217±2375	2243±1414	121.36± 47.49	<0.00001[a]* <0.00001[b]* 0.0028[c]*
Dimensions of systolic function	LVEDD (mm/M2)	42.1±6.79	40.13±5.99	36.36±5.18	0.0247[a]* 0.0496[b]* 0.3894[c]
	LVESD (mm/M^2)	27.7±5.58	24.63±4.39	21.91±3.11	0.0100[a]* 0.1271[b] 0.0819[c]
	LVEF %	63.9±6.30	68.93±6.91	69.36±7.30	0.1621[a] 0.6534[b] 0.0487[c]*
	FS%	35.2±4.96	39.0±5.68	38.64±6.20	0.3128[a] 0.4240[b] 0.0670[c]
Dimensions of diastolic function	E wave (cm/second)	114.3±17.37	115.93±18.78	99.64±12.56	0.0167[a]* 0.002[b]* 0.8098[c]
	A wave (cm/second)	61.2±26.05	55.57±16.31	55.73±15.43	0.3266[a] 0.4236[b] 0.4236[c]
	E/A ratio	2.148±0.90	2.22±0.62	1.87±0.41	0.3761[a] 0.0888[b] 0.7894[c]
(Tei LV)		0.48±0.55	0.24±0.14	0.20±0.05	0.0392[a]* 0.5241[b] 0.0327[c]*
Pulmonary artery systolic pressure		40.5±10.47	36.97±8.60	31.91±6.25	0.03097[a]* 0.1041[b] 0.2932[c]

[Table/Fig-4]: Thyroid function status in the studied cases in relation to laboratory and echocardiographic parameters.
*significant; a: impaired vs. control; b: normal function vs. control; c: impaired vs. normal function)
TSH: Thyroid simulating hormone; FT4: Free thyroxin; LVEDD: Left ventricle end diastolic diameter; LVESD: Left ventricle end systolic diameter; LVEF: Left ventricular ejection fraction; FS: Fractional shortening; E wave: Early diastolic flow velocity; A wave: Late diastolic flow velocity

Compared to controls; all βTM cases had significant higher mitral and filling velocity E-wave velocity (p-value<0.05) and βTM cases with impaired thyroid function had significant larger dimensions of LVEDD and LVESD, significant higher LV Tei, significant higher pulmonary artery pressure and significant lower EF % [Table/Fig-4].

With increasing age; β-TM cases aged above nine years showed significant increase in LVEDD, β-TM cases with impaired thyroid function exhibited significantly higher LVESD in comparison to normal (p-value=0.001), and serum ferritin (p-value=0.01) [Table/Fig-5].

The group with a duration of blood transfusion therapy more than six years; showed significantly larger dimensions of LVEDD (p-value=0.002), LVESD (p-value=0.018) [Table/Fig-6].

βTM cases with frequent blood transfusion every two weeks have significant increase in serum ferritin levels compared to non frequent blood transfusion cases [Table/Fig-7].

Parameter (Mean±SD)		βTM Cases Age		t-test	
		<9 years	>9 years	t	p-value
TSH	(uIU/mL)	2.77±1.48	2.80±1.25	0.076	0.940
FT4	(p mol/L)	16.99±4.25	17.89±3.73	0.814	0.421
Ferritin	(ug/dl)	1765.6±1202.0	3246.6±2036.3	2.6694	0.011*
Dimensions of systolic function	LVEDD (mm/M²)	36.65±3.32	43.57±6.18	-4.184	0.001**
	LVESD (mm/M²)	22.65±2.45	27.43±5.18	-3.524	0.001**
	LVEF %	68.47±5.95	67.09±7.82	0.610	0.546
	FS%	39.00±4.62	37.35±6.39	0.905	0.371
Dimensions of diastolic function	E wave (cm/sec)	116.88±16.90	113.22±22.51	0.563	0.576
	A wave (cm/sec)	56.71±18.05	57.30±19.91	-0.098	0.923
	E/A ratio	2.25±0.72	2.16±0.67	0.429	0.670
Tei LV		0.31±0.46	0.27±0.12	0.415	0.681
Pulmonary artery systolic pressure		39.59±8.56	36.41±9.64	1.072	0.291

[Table/Fig-5]: Thyroid hormones, ferritin and echocardiographic parameters in the studied βTM cases in relation to age.
*significant; TSH- Thyroid simulating hormone; FT4- Free thyroxin; LVEDD- Left ventricle end diastolic diameter; LVESD- Left ventricle end systolic diameter; LVEF- Left ventricular ejection fraction; FS- Fractional shortening; E- Early diastolic flow velocity; A- Late diastolic flow velocity

Parameter (Mean±SD)		βTM cases duration of blood transfusion therapy (years)		t-test	
		<6 years	>6 years	t	p-value
TSH	(uIU/mL)	2.74±1.19	2.88±1.65	0.323	0.749
FT4	(p mol/L)	17.50±2.45	17.50±4.50	0.042	0.967
Ferritin	(ug/dl)	2031.6±1277.5	2942.7±2024.1	-1.482	0.1467
Dimensions of systolic function	LVEDD (mm/M2)	36.38±3.38	42.67±6.20	3.402	0.002*
	LVESD (mm/M2)	22.85±2.85	26.63±5.14	2.467	0.018*
	LVEF %	67.62±6.41	67.70±7.44	0.037	0.971
	FS%	38.08±4.92	38.04±6.12	0.020	0.984
Dimensions of diastolic function	E wave (cm/sec)	115.00±20.72	114.67±20.28	0.048	0.962
	A wave (cm/sec)	55.69±18.38	57.70±19.46	0.311	0.757
	E/A ratio	2.25±0.75	2.17±0.67	0.334	0.740
Tei LV		0.23±0.15	0.32±0.37	0.911	0.369
Pulmonary artery systolic pressure		38.54±8.78	37.42±9.56	0.353	0.726

[Table/Fig-6]: Thyroid function, serum ferritin and echo parameters in βTM patients in relation to duration of blood transfusion therapy.
*significant; TSH- Thyroid simulating hormone; FT4, Free thyroxin; LVEDD- Left ventricle end diastolic diameter; LVESD- Left ventricle end systolic diameter; LVEF- Left ventricular ejection fraction; FS- Fractional shortening; E- Early diastolic flow velocity; A- Late diastolic flow velocity

The regular use of iron chelating agent in βTM patients was more frequent in younger age patients but without significant effects on serum ferritin and Echo parameters, thyroid function and serum ferritin [Table/Fig-8].

Splenectomized patients had significant older age and higher FT4 levels [Table/Fig-9].

βTM cases with serum ferritin level above (2500 ug/dL) showed significant prolangation in E wave (p-value=0.029) [Table/Fig-10].

Spearman's correlation in βTM patients; FT4 showed significant negative correlation with TSH and Tei LV, whereas ferritin showed significant positive correlation with TSH, LVEDD and LVESD [Table/Fig-11,12].

Parameter (Mean±SD)		Blood transfusion Frequency		t-test	
		Not frequent	Frequent	t	p-value
Age	(years)	10.17±3.1	8.42±3.69	-1.19	0.2439
TSH	(uIU/mL)	2.75±0.88	2.79±1.42	0.068	0.946
FT4	(p mol/L)	16.99±4.25	17.50±3.99	0.315	0.754
Ferritin	(ug/dL)	2456±1731	4203.5±1887	2.165	0.039*
Dimensions of systolic function	LVEDD (mm/M²)	40.21±6.13	42.57±6.45	0.917	0.365
	LVESD (mm/M²)	25.27±4.82	26.00±5.23	0.358	0.722
	LVEF %	67.24±6.91	69.71±7.83	0.841	0.406
	FS%	37.79±5.66	39.29±6.18	0.627	0.535
Dimensions of diastolic function	E wave (cm/sec)	112.42±21.19	125.86±8.53	1.635	0.110
	A wave (cm/sec)	55.61±19.69	63.86±13.78	1.050	0.300
	E/A ratio	2.23±0.72	2.06±0.56	0.585	0.562
Tei LV		0.31±0.34	0.17±0.08	1.038	0.306
Pulmonary artery systolic pressure		37.47±9.72	39.29±6.75	0.468	0.642

[Table/Fig-7]: Thyroid hormones, serum ferritin and echo parameters in βTM patients in relation to blood transfusion frequency.
TSH-Thyroid simulating hormone; FT4-Free thyroxin; LVEDD-Left ventricle end diastolic diameter; LVESD-Left ventricle end systolic diameter; LVEF- Left ventricular ejection fraction; FS- Fractional shortening; E- Early diastolic flow velocity; A- Late diastolic flow velocity

Parameter (Mean±SD)		Iron chelating agents		T-test	
		Irregular	Regular	t	p-value
Age	(years)	11.27±2.52	8.25±3.27	2.792	0.01*
TSH	(uIU/mL)	2.97±1.37	2.6±1.3	0.864	0.393
FT4	(p mol/L)	16.47±3.73	18.40±4.12	1.441	0.158
Ferritin	(ug/dL)	3426±2246	2166±1114	1.892	0.069
Dimensions of systolic function	LVEDD (mm/M²)	42.15±6.07	39.10±6.03	1.595	0.119
	LVESD (mm/M²)	26.00±5.05	24.80±4.65	0.782	0.439
	LVEF %	68.80±7.53	66.55±6.50	1.012	0.318
	FS%	38.50±6.08	37.60±5.40	0.495	0.624
Dimensions of diastolic function	E wave (cm/second)	118.00±19.31	111.55±20.96	1.012	0.318
	A wave (cm/second)	58.05±21.80	56.05±16.01	0.331	0.743
	E/A ratio	2.25±0.75	2.15±0.63	0.436	0.666
Tei LV		0.24±0.15	0.34±0.41	1.001	0.324
Pulmonary artery systolic pressure		39.95±10.49	35.75±7.50	1.443	0.157

[Table/Fig-8]: Thyroid hormones, serum ferritin and echo parameters in βTM patients in relation to iron chelating agents.
TSH-Thyroid simulating hormone; FT4-Free thyroxin; LVEDD-Left ventricle end diastolic diameter; LVESD- Left ventricle end systolic diameter; LVEF- Left ventricular ejection fraction; FS- Fractional shortening; E- Early diastolic flow velocity; A- Late diastolic flow velocity

DISCUSSION

Though iron chelating therapy has improved outcomes noticeably, cardiac failure remains an important cause of death in βTM [11]. Various pathologies were proposed including chronic anaemia, tissue hypoxia, myocarditis and iron overload, with subsequent diastolic then systolic dysfunction. Moreover; iron overload in the lungs leading to elevated pulmonary resistance, RV dilatation and dysfunction result in heart failure [12].

In this study, 25% βTM had impaired thyroid function {primary (n=1, 2.5%); subclinical (n=5, 12.5%); and central (secondary) hypothyroidism (n=4, 10%)}. The severity of endocrine disease was associated with an increase of ferritin levels. In βTM thyroid dysfunction was reported in variable prevalence in different cohorts [13-15]. This discrepancy was related to genetic, geographic, cultural, economic factors, methods used for thyroid function, ages, different amount and quality of blood transfusion, different

Parameter (Mean ± SD)		Splenectomy		t-test	
		No	Yes	t	p-value
Age	(years)	8.79±3.1	11.73± 2.15	-3.121	0.004*
TSH	(uIU/ml)	2.43±0.99	3.03±1.34	1.488	0.146
FT4	(p mol/L)	16.36±3.96	19.23±3.67	-2.289	0.028*
Ferritin	(ug/dl)	2515±1937	3231±1938	-1.07	0.292
Dimensions of systolic function	LVEDD (mm/M²)	39.36±5.79	42.73±6.39	1.716	0.094
	LVESD (mm/M²)	24.52±3.91	26.87±5.93	1.512	0.139
	LVEF %	67.96±5.55	67.20±9.21	0.327	0.746
	FS%	38.40±4.32	37.47±7.61	0.497	0.622
Dimensions of diastolic function	E wave (cm/sec)	114.12±19.80	115.87±21.40	0.262	0.795
	A wave (cm/sec)	56.16±15.40	58.53±24.20	0.380	0.706
	E/A ratio	2.14±0.59	2.29±0.83	0.643	0.524
Tei LV		0.30±0.39	0.28±0.13	0.183	0.856
Pulmonary artery systolic pressure		37.16±8.27	38.93±10.92	0.570	0.572

[Table/Fig-9]: Thyroid hormones, serum ferritin and echo parameters in βTM patients in relation to splenectomy.
*significant; TSH- Thyroid simulating hormone; FT4- Free thyroxin; LVEDD- Left ventricle end diastolic diameter; LVESD- Left ventricle end systolic diameter; EF- Left ventricular ejection fraction. FS- Fractional shortening; E- Early diastolic flow velocity; A- Late diastolic flow velocity

Parameter (Mean ± SD)		Serum ferritin level (µg/dl)		t-test	
		<2500	> 2500	t	p-value
TSH	(uIU/ml)	2.55±1.45	3.15±1.10	1.39	0.171
FT4	(p mol/L)	16.97±4.06	17.74±4.06	-0.582	0.564
Dimensions of systolic function	LVEDD (mm/M²)	39.54±5.95	42.24±6.20	-1.38	0.176
	LVESD (mm/M²)	24.5±3.76	26.71±5.43	-1.146	0.151
	LVEF %	68.04±5.61	67.10±7.91	0.399	0.691
	FS%	38.5±4.62	37.43±6.34	-0.607	0.548
Dimensions of diastolic function	E wave (cm/sec)	110.46±20.10	123.13±11.90	-2.264	0.029*
	A wave (cm/sec)	54.29±14.76	61.19±23.77	-1.134	0.264
	E/A ratio	2.14±0.58	2.22±0.74	-0.668	0.508
Tei LV		0.32±0.38	0.24±0.12	-0.825	0.414
Pulmonary artery systolic pressure		36.58±8.59	39.4±9.13	-1.060	0.296

[Table/Fig-10]: Thyroid hormones and echo parameters among the βTM patients in relation to serum ferritin level.
*significant; TSH- Thyroid simulating hormone; FT4- Free thyroxin; LVEDD- Left ventricle end diastolic diameter; LVESD- Left ventricle end systolic diameter; EF- Left ventricular ejection fraction; FS- Fractional shortening; E- Early diastolic flow velocity; A- Late diastolic flow velocity

medications, type and dosages of iron-chelating therapy.

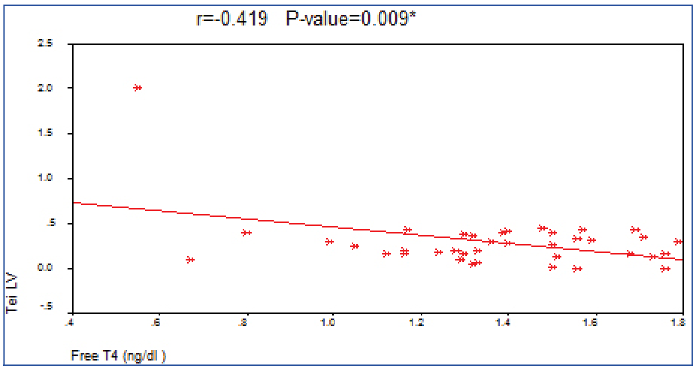
In this study; heart rate was higher in βTM, in contrast Garadah TS and colleagues reported lower heart rate in βTM as single clinical manifestation of hypothyroidism [16], and Lala R and colleagues found marked increase in ferritin in non-splenectomized cases [17]. Belhoul KM and coworkers stated that endocrinopathy is common in βTM patients either with high serum ferritin levels or those splenectomized, however; we detect non-significant correlation between splenectomy and hypothyroidism [18].

The mean patient's age was (9.51±3.26) and hypothyroidism is likely to be found in older age [19]. In contrast, Gulati R and colleagues reported the probability of endocrine dysfunction at an earlier age in developing countries [20].

In this study; LV dimensions (LVEDD and LVESD) were significantly higher in βTM but without changes in LVFS or EF% that indicated preserved systolic function; this was in agreement with [16,21-23]. These changes were evident in cases with older age, higher serum ferritin and longer duration of transfusion therapy; this was

βTM cases parameters		TSH		Free T4		Ferritin	
		r	p-value	r	p-value	r	p-value
TSH		-	-	-0.3345	0.0349*	0.3498	0.0269*
Free T4		-0.3345	0.0349*	-	-	0.0132	0.9356
Ferritin	(ug/dl)	0.280	0.0797	-0.018	0.9171	-	-
Dimensions of systolic function	LVEDD (mm/M²)	0.059	0.716	-0.064	0.694	0.3257	0.0403*
	LVESD (mm/M²)	0.108	0.508	-0.025	0.877	0.3689	0.0192*
	LVEF %	-0.095	0.562	-0.050	0.761	-0.151	0.3523
	FS%	-0.121	0.455	-0.075	0.644	-0.2082	0.1974
Dimensions of diastolic function	E wave (cm/sec)	0.094	0.564	0.082	0.616	-	-
	A wave (cm/sec)	0.014	0.929	-0.086	0.597	-	-
	E/A ratio	0.130	0.425	0.119	0.466	0.02807	0.8635
Tei LV		-0.186	0.265	-0.419	0.009*	-0.0251	0.8781
Pulmonary artery systolic pressure		0.239	0.143	-0.107	0.516	0.1598	0.3247

[Table/Fig-11]: Correlation between thyroid hormones, ferritin and echo parameters among the βTM patients.
*significant; TSH- Thyroid simulating hormone; FT4- Free thyroxin; LVEDD- Left ventricle end diastolic diameter; LVESD- Left ventricle end systolic diameter; EF- Left ventricular ejection fraction. FS- Fractional shortening; E wave- Early diastolic flow velocity; A wave- Late diastolic flow velocity



[Table/Fig-12]: Correlation between FT4 and the myocardial performance index (Tei LV) among the βTM cases.

consistent with previous studies [24,25].

Moreover, Garadah TS and colleagues revealed a restrictive LV diastolic pattern with preserved LV systolic function [16].

De Sanctis V and colleagues established that cardiac abnormalities were common in βTM patients with severe iron overload and poor compliance to DFX and an improvement of LVEF was observed after either an intensive chelation therapy or thyroxin replacement therapy with regular iron chelation therapy [14].

In this study, EF% was significantly shorter in βTM cases with impaired thyroid function compared to cases with euthyroid function. However, the overall normal EF% indicates that βTM patients had minimal deleterious effect of iron overload on myocardial systolic function in spite of high ferritin level. This may also explain the absence of heart failure or significant valve diseases in the current study population. In contrast, Magri D and colleagues detected an impairment of myocardial function in βTM patients even in young, asymptomatic and well-chelated cases [24].

In this study, βTM cases had significantly higher peak flow velocity in early diastole (E-wave); while late (atrial or A-wave) peaks of flow velocity and the ratio between the early and late (atrial) peaks of flow velocity showed insignificant changes. Tei LV and pulmonary artery pressure were significantly increased in βTM cases with impaired thyroid function, age above (nine years) and high serum ferritin. These results were in line with a study by Gulati R et al., [20] and partially consistent with Kremastinos DT et al., [26] who revealed altered diastolic function by an increase of both early and late peak trans-mitral flow velocity without change of the E/A ratio.

In contrast, other studies [9,27,28] reported an increase in peak flow velocity at early diastole E-wave and the E/A ratio in βTM cases, while Yaprak and colleagues revealed significant higher E-wave, E/A ratio, and lower A-wave velocity suggestive of a restrictive pattern [29].

In this study, Tei LV was significantly high in βTM cases with impaired thyroid function compared to controls or cases with euthyroid state, suggestive of early left ventricular dysfunction. This result was in line with Frommelt PC et al., [30].

In this study, the mean pulmonary pressure was insignificantly higher in βTM. In contrast Hahalis G and colleagues revealed pulmonary hypertension in βTM patient's resulting from pulmonary haemosiderosis [11].

In this study, we found insignificant difference in systolic and diastolic functions in βTM patients in relation to Hb level, this finding consistent with Yaprak I et al., [29].

Bosi G and colleagues found significant weak negative correlation between LVEF% and serum ferritin and he reported that the overall cardiovascular prognosis was good if the serum ferritin is below 2500 ng/dL. The higher mean age of the patients in Bosi's study might be the responsible for the detection of LV systolic dysfunction [27].

However, Iarussi D reported right sided heart failure in 16% of βTM patients with high serum ferritin (>2500 ng/mL) [31,32]. Also, Wood JC and colleagues found that cardiac risk is conveyed by positive iron balance over a prolonged period of time [25].

In this study, we found non-significant impairment in diastolic function parameters. In contrast, Silvilairat S and colleagues found that LV diastolic dysfunction was correlated to serum ferritin as LV diastolic dysfunction was absent in patients with serum ferritin (<2500 ng/mL) and was present in patients with serum ferritin (>5000 ng/mL) [32]. It seems that myocardial disease goes through an impaired relaxation stage before development of systolic dysfunction. This maybe due to iron overload and increased stiffness of the LV wall [9].

In the current study, although all βTM cases documented receiving iron chelation therapy, serum ferritin was more than 35 times higher in the βTM cases compared with controls, therefore, the iron burden was severe, indicating suboptimal dosage and/or compliance. These finding confirms that iron overload mediate the impaired diastolic function leading to stiffness of the myocardial wall but with well-preserved LV systolic function, this consistent with Aydinok Y et al., and Garadah T et al., [5,33].

In this study, significance positive correlation between ferritin and TSH, LVEDD and LVESD was established and significance negative correlation between FT4 with TSH and myocardial performance index (Tei LV) was found.

LIMITATION

The small sample size used is the major limitation of the current study. Therefore, it is considered a pilot study and further studies on a larger cohort are warranted.

CONCLUSION

Improper chelation therapy results in cardiac dysfunction and a considerable proportion have thyroid dysfunction, therefore, all transfusion dependent βTM children needs optimal early use of chelation therapy, wise blood transfusion and periodic evaluation of thyroid and cardiac functions. Thyroxin replacement therapy may be considered in βTM cases having combined iron overloaded and subclinical hypothyroidism or cases with poor response to chelation therapy.

REFERENCES

[1] El-Beshlawy A, Youssry I. Prevention of haemoglobinopathies in Egypt. Haemoglobin. 2009;33:S14-20.

[2] Herbert L, Muncie JR, James S, Campbell M. Alpha and beta thalassaemia. Am Fam Physician. 2009;80(4):339-44.

[3] Filosa A, Di Maio S, Aloj G, Acampora C. Longitudinal study on thyroid function in patients with thalassaemia major. J Paediatr Endocrinol Metab. 2006;19:1397-404.

[4] Thomas AS, Garbowski M, Ang AL, Shah FT, Walker JM, Moon JC, et al. A decade follow-up of a thalassaemia major (TM) cohort monitored by Cardiac Magnetic Resonance imaging (CMR): significant reduction in patients with cardiac iron and in total mortality. Blood. 2010;116(21):abst 1011.

[5] Aydinok Y, Porter JB, Piga A, Elalfy M, El-Beshlawy A, Kilinç Y, et al. Prevalence and distribution of iron overload in patients with transfusion-dependent anaemias differs across geographic regions: results from the CORDELIA study. Eur J Haematol. 2015;95(3):244-53.

[6] Tsironi M, Korovesis K, Farmakis D, Deftereos S, Aessopos A. Hypocalcemic heart failure in thalassemic patients. Int J Hematol. 2006;83:314-17.

[7] Aessopos A, Berdoukas V, Tsironi M. The heart in transfusion dependent homozygous thalassaemia today- prediction, prevention and management. Journal compilation. 2008;80:93-106.

[8] Abdulzahra MS, Al-Hakeim HK, Ridha MM. Study of the effect of iron overload on the function of endocrine glands in male thalassaemia patients. Asian Journal of Transfusion Science. 2011;5(2):127-31.

[9] Gharzuddine WS, Kazma HK, Nuwayhid IA, Bitar FF, Koussa SF, Moukarbel GV, et al. Doppler characterization of left ventricular diastolic function in beta-thalassaemia major. Evidence for an early stage of impaired relaxation. Eur J Echocardiogr. 2002;3(1):47-51.

[10] Aessopos A, Deftereos S, Tsironi M, Karabatsos F, Yousef J, Fragodimitri C, et al. Predictive echo-Doppler indices of left ventricular impairment in β-thalassemic patients. Ann Hematol. 2007;86:429-34.

[11] Hahalis G, Alexopoulos D, Kremastinos DT, Zoumbos NC. Heart failure in beta-thalassaemia syndromes: a decade of progress. Am J Med. 2005;118:957-67.

[12] Hahalis G, Manolis AS, Apostolopoulos D, Alexopoulos D, Vagenakis AG, Zoumbos N. Right ventricular cardiomyopathy in beta-thalassaemia major. Eur Heart J. 2002;23:147-56.

[13] Borgna-Pignatti C, Rugolotto S, De Stefano P, Zhao H, Cappellini MD, Del Vecchio GC, et al. Survival and complications in patients with thalassaemia major treated with transfusion and deferoxamine. Haematologica. 2004;89(10):1187-93.

[14] De Sanctis V, De Sanctis E, Ricchieri P, Gubellini E, Gilli G, Gamberini MR. Mild subclinical hypothyroidism in thalassaemia major: prevalence, multigated radionuclide test, clinical and laboratory long-term follow-up study. Pediatr Endocrinol Rev. 2008;6 Suppl 1:174-80.

[15] Abdel-Razek AR, Abdel-Salam A, El-Sonbaty MM, Youness ER. Study of thyroid function in Egyptian children with β-thalassaemia major and β-thalassaemia intermedia. J Egypt Public Health Assoc. 2013;88(3):148-52.

[16] Garadah TS, Mahdi NA, Jaradat AM, Hasan ZA, Nagalla DS. Thyroid function status and echocardiographic abnormalities in patients with beta thalassaemia major in Bahrain. Cardiology. 2013;(7):21-27.

[17] Lala R, Chiabotto P, Di Stefano M, Isaia GC, Garofalo F, Piga A. Bone density and metabolism in thalassaemia. J Pediatr Endocrinol Metab. 2005;11:785-90.

[18] Belhoul KM, Bakir ML, Saned MS, Kadhim AM, Musallam KM, Taher AT. Serum ferritin levels and endocrinopathy in medically treated patients with β thalassaemia major. Ann Hematol. 2012;91(7):1107-14.

[19] Abdalla M, Fawzi M, Salem R, El-Banna N, Tayyem RF, Ahmad IM. Increased oxidative stress and iron overload in jordanian β-thaassemic children. Haemoglobin. 2011;35:67-79.

[20] Gulati R, Bhatia V, Agarwal SS. Early onset of endocrine abnormalities in beta-thalassaemia major in a developing country. J Pediatr Endocrinol Metab. 2000;13(6):651-56.

[21] Khalifa AS, Ayoub AM, Al-Shabrawy L. Cardiac changes in Beta-thalassaemia major and effect of treatment. Egypt J Ped. 1989;6:415.

[22] Desideri A, Scatolin G, Gobellini, Cavuto F. Left ventricular function in thalassaemia major: protective effect of desferoxamine. Can J Cardiol. 1994;10(1):63-66.

[23] Hui L, Leung Mp, Ha SY, Chau AK, Cheung YF. Early left ventricular dysfunction and chelation therapy in thalassaemia major. Heart. 2003;89:669-70.

[24] Magr` D, Sciomer S, Fedele F, Gualdi G, Casciani E, Pugliese P, et al. Early impairment of myocardial function in young patients with beta-thalassaemia major. Eur J Haematol. 2008;80(6):515-22.

[25] Wood JC. Cardiac iron across different transfusion-dependent diseases. Blood Rev. 2008;22:14-21.

[26] Kremastinos DT, Tsiapras DP, Tsetsos GA, Rentoukas EI, Vretou HP, Toutouzas PK. Left ventricular diastolic Doppler characteristics in Thalassaemia Major. Circulation. 1993;88:1127-35.

[27] Bosi G, Crepaz R, Gamberini MR, Fortini M, Scarcia S, Bonsante E, et al. Left ventricular remodeling and systolic and diastolic function in young adults with b thalassaemia major: a Doppler echocardiographic assessment and correlation with haematological data. Heart. 2003;89:762-66.

[28] Mamtani M, Kulkarni H. Influence of iron chelator on myocardial iron and cardiac function in transfusion dependent thalassaemia: a systematic review and meta-analysis. Br J Haematol. 2008;141:882-90.

[29] Yaprak I, Aksit S, Ozturk C, Bakiler AR, Dorak C, Turker M. Left ventricle diastolic abnormalities in children with beta-thalassaemia major: Doppler echocardiographic study. Turk J Pediatr. 1988;40(2):201-19.

[30] Frommelt PC, Ballweg JA, Whitstone BN, Frommelt MA. Usefulness of Doppler tissue imaging analysis of tricuspid annular motion for determination of right ventricular function in normal infants and children. Am J Cardiol. 2002;89:610-13.
[31] Iarussi D, Di Salvo G, Pergola V, Coppolino P, Tedesco MA, Ratti G, et al. Pulsed Doppler tissue imaging and myocardial function in thalassaemia major. Heart Vessels. 2003;18:1-6.
[32] Silvilairat S, Sittiwangkul R, Pongprot Y, Charoenkwan P, Phornphutkul C. Tissue Doppler echocardiography reliably reflects severity of iron overload in paediatric patients with b thalassaemia. Eur J Echocardiogr. 2008;9:368-72.
[33] Garadah T, Kassab S, Mahdi N, Abu-Taleb A, Jamsheer A. Pulsed and tis¬sue Doppler echocardiographic changes in patients with thalassaemia major. Clinical Medicine: Blood Disorders. 2010;3:1-8

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