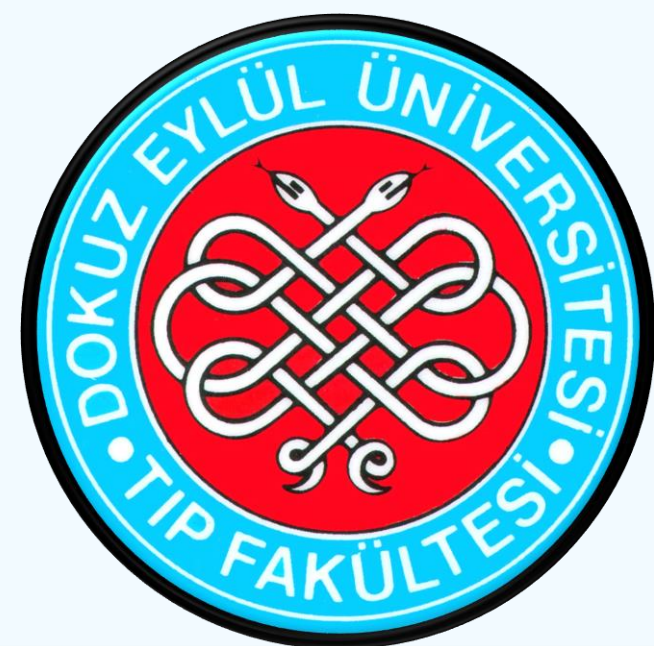


The Effect of L-thyroxine Treatment on Left Ventricular Functions in Children with Subclinical Hypothyroidism



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Background

Definition of subclinical hypothyroidism (SH): Elevated TSH and normal serum fT4 concentrations.

- The symptoms and signs of SH are often non-specific and subtle.
- Thyroid disorders cause changes in cardiac contractility, myocardial oxygen consumption, cardiac output, and blood pressure.
- Left ventricular (LV) diastolic dysfunction in adults with SH and beneficial effects of thyroid hormone replacement on systolic and diastolic functions in adults with SH has been documented
- The presence of similar alterations in children with SH is still under debate.

Aim

This is the first study to evaluate cardiac functions and the effects of L-T4 replacement in otherwise healthy children with SH. With this study, we aimed to search an evidence for suggesting treatment for childhood SH by evaluating LV functions before and after L-T4 replacement by using M-mode echocardiography and tissue Doppler echocardiography (TDE).

Methods

- Children with SH and euthyroid healthy children (control group) were enrolled in the study.
- Only patients with stable elevated TSH and normal fT4 levels in at least two different measurements 4-6 weeks apart were included in the study.
- At baseline and six months after euthyroidism was achieved M-mode and TDE were performed and LV functions were evaluated.
- Pre-treatment parameters of the SH group were compared with those of controls and post-treatment parameters.

Exclusion Criteria;

Cardiovascular and respiratory diseases, hepatic or renal dysfunction, diabetes mellitus, malignancy and obesity were excluded in both the SH and control groups.

Initiation of L-thyroxin treatment

- In the SH group, L-T4 treatment was started at a dose of 2µg/kg/d and the dose was titrated every 4 weeks until a normal TSH level is maintained.
- Six months after euthyroid state was achieved echocardiographic examination (*Conventional two-dimensional (2D) Doppler echocardiography and Pulsed TDE*) was repeated and the results were compared with the baseline values.

Statistical analysis

- Statistical comparison between groups was performed with the independent Student's T test.
- Chi-square tests were used for the comparison of categorical variables.
- Parameters before and after L-T4 treatment were compared by paired samples T test.

Table 1. M-mode left ventricular echocardiographic parameters of the SH and control group before and after L-thyroxin replacement therapy

	*SH Group (N=31)	*Control Group (N=32)	*P	&After Treatment	&p
Morphologic parameters					
LVEDD (cm)	3.90±0.63	3.9±0.4	0.864	4.12±0.72	0.017
LVESD (cm)	2.26±0.43	2.33±0.26	0.633	2.49±0.49	0.006
IVSD (cm)	0.71±0.09	0.62±0.08	0.014	0.71±0.12	1.0
LVPWD (cm)	0.68±0.16	0.66±0.19	0.314	0.65±0.11	0.237
LVM (g)	78.02±34.45	66.17±22.23	0.099	80.92±35.12	0.112
LVMI (g/m ^{2.7})	28.6±6.3	24.9±5.4	0.017	28.01±5.22	0.447
Systolic parameters					
FS (%)	39.66±3.86	38.85±5.63	0.591	38.71±4.33	0.439
EF (%)	70.96±4.56	69.59±5.75	0.481	69.96±5.35	0.397
ET (ms)	271.25±26.29	275.22±18.23	0.416	279.37±28.39	0.286
Diastolic parameters					
Peak E (cm/s)	97.68±12.56	94.7±12.73	0.741	94.35±14.28	0.187
Peak A (cm/s)	66.23±11.89	62.48±11.50	0.342	62.28±15.58	0.100
E/A ratio	1.52±0.37	1.55±0.32	0.507	1.58±0.41	0.253
MDT (ms)	124.9±14.9	127.37±23.39	0.597	132.10±28.60	0.170
Global ventricular (systolic and diastolic) performance					
MPI	0.29±0.14	0.28±0.10	0.681	0.27±0.13	0.376

Results

A total of 31 children with SH (SH group, mean age of 10.3±3.4 years, 19 male, 17 prepubertal) and 32 euthyroid healthy children (control group, mean age of 10.8±2.9 years, 13 male, 15 prepubertal) were enrolled in this study. There was no statistically significant difference between the groups regarding age, gender, puberty, BMI, BMI-SDS, heart rate, SBP and DBP (P<0,05). Euthyroid state was reached in a median duration of 35 days (interquartile range: 22.5). The mean treatment dose of L-T4 was 1.93±0.37 µg/kg/d when echocardiographic examination was repeated.

Conventional (M-mode) Doppler echocardiography parameters

At baseline SH patients had slightly higher IVS thickness and LVMI than the control group (p=0.001; p=0.017, respectively); however other parameters derived from conventional Doppler echocardiography were similar in both groups (Table 1). Results of M-mode echocardiography and pulsed wave Doppler measurements of the SH group before and after L-T4 therapy are shown in Table 1. At 6 months, L-T4 treated patients showed a significant increase in some of LV morphologic parameters (LVESD and LVEDD) as absolute values while there was no significant change in z-scores (LVESD z score -0.69±0.8 & -0.51±1, p=0.138; LVEDD z score -0.33±1 & -0.16±1.1, p=0.427). Besides, there was no change in other M-mode echocardiography-derived parameters.

Pulsed TDE parameters

Compared to the control group, SH patients exhibited significant impairment in some of the diastolic (lower E'm, higher E/ E'm, longer IVRTm), systolic (longer IVCTm) and global LV functional parameters (higher MPI) in LM localization, in addition to longer ET, IVRTm, IVCTm and higher MPI in the IVS localization (Table 2). After 6 months of therapy, L-T4 treated patients showed significant improvements in systolic (shortening of IVCTm, p<0.001) and diastolic (shortening of IVRTm, p<0.001) parameters that resulted in a significant increase in global ventricular performance (decreased MPI, p<0.001) (Table 2).

Table 2. Pulsed TDI parameters of the SH and control groups; before and after thyroid hormone replacement therapy

	*SH Group (N=31)	*Control Group (N=32)	*P	&After Treatment	&p
Lateral localizations of the mitral annulus					
Systolic parameters					
S _m (cm/s)	10.66±3.06	10.10±2.54	0.978	11.10±3.83	0.109
IVCT _m (ms)	38.45±7.60	32.37±5.00	<0.001	35.03±7.37	0.001
ET (ms)	262.21±22.28	287.71±23.80	0.002	277.53±22.15	0.058
Diastolic parameters					
E' _m (cm/s)	18.32±3.16	20.79±4.81	0.036	18.14±4.73	0.922
A' _m (cm/s)	6.80±1.25	7.32±2.14	0.142	7.79±2.53	0.034
E' _m /A' _m ratio	2.78±0.72	2.96±0.73	0.911	2.56±0.96	0.105
IVRT _m (ms)	47.60±6.49	40.58±5.46	<0.001	41.89±8.78	<0.001
E/E' _m	5.30±0.93	4.86±1.01	0.035	4.97±2.95	0.251
Global ventricular performance					
MPI	0.33±0.06	0.26±0.03	<0.001	0.28±0.06	<0.001
Interventricular septum					
Systolic parameters					
S _m (cm/s)	8.29±1.29	8.06±1.27	0.794	7.99±1.95	0.622
IVCT _m (ms)	41.0±6.85	32.72±5.35	<0.001	36.63±7.6	0.001
ET (ms)	256.78±26.20	287.42±23.58	<0.001	273.47±15.90	0.009
Diastolic parameters					
E' _m (cm/s)	12.43±2.47	13.37±3.01	0.190	13.38±4.66	0.260
A' _m (cm/s)	6.87±2.03	6.36±1.69	0.779	7.00±3.07	0.429
E' _m /A' _m ratio	1.92±0.54	2.26±0.93	0.217	2.06±0.78	0.705
IVRT _m (ms)	50.1±8.43	39.82±5.90	<0.001	44.03±8.26	0.001
Global ventricular performance					
MPI	0.35±0.06	0.25±0.04	<0.001	0.29±0.05	<0.001

* Student's T test, & paired samples T test

Conclusions

In conclusion, this is the first study to investigate the effect of L-T4 replacement on LV functions of children with SH.

- Our data suggest that SH in childhood is associated with pre-clinical alterations in both systolic and diastolic functions and after L-T4 replacement a significant improvement in global LV performance was revealed.
- However, since SH is usually a self-limiting process, these improvements in LV functions may simply be associated with the natural course of the disease and/or physiological linear growth of the children.
- Therefore, our results should not be interpreted as a strong indication for the treatment of SH in childhood and they need to be confirmed with larger and long-term studies investigating the effect of L-T4 on myocardial functions in childhood SH.