

## Metabolic and Cardiovascular Aspects of Subclinical Hypothyroidism: Effects of L-Thyroxin Replacement Therapy

Mehtap Evran<sup>1\*</sup>, Murat Sert<sup>1</sup>, Tamer Tetiker<sup>1</sup>, Murat Çaylı<sup>2</sup>

<sup>1</sup>Cukurova University Medical Faculty, Department of Internal Medicine, Division of Endocrinology Adana, Turkey

<sup>2</sup>Adana Numune Education and Research Hospital, Department of Cardiology, Adana, Turkey

### Abstract

**Background:** Subclinical hypothyroidism (SH) is a common clinical issue, presented with high serum TSH and normal T4, T3 levels. Various clinical and metabolic derangements were reported related to SH. L-T4-replacement is a challenge in daily practice. We investigated the efficacy of L-T4-replacement on certain metabolic and cardiovascular parameters in subjects with SH.

**Methods:** Fifty-three (40 female; 13 male) subjects were included. Of the 53 subjects, 29 were randomly given L-T4 replacement, 24 were followed as control group through 6-months. Before L-T4 replacement (basal) and at the end of the study; symptoms, physical examination, serum metabolic parameters, Holter ECG and trans-thoracic echocardiography were performed. Two groups were compared.

**Results:** Mean age of the patients was  $44.02 \pm 13.9$ ; body mass index  $29.4 \pm 6.4$  kg/m<sup>2</sup>. In the T4-replacement group, there was a significant difference between serum TSH and FT3 levels compared to the basal measurements ( $p = 0.005$  and  $p = 0.017$ ). LDL-cholesterol levels of the replacement group were not changed significantly, but of the control group significantly increased ( $p=0.01$ ). Mean ejection fraction (EF) did not show significant change at both basal and 6-month. Peak transmitral early diastolic flow speed (E) decreased in the control group ( $p = 0.013$ ). Peak transmitral late diastolic flow speeds (Em/Am) of the controls were found to be decreased compared to the basal ratio ( $p = 0.005$ ). Isovolumetric relaxation times (IVRT) of both groups were prolonged at the time of basal measurements ( $123 \pm 45.8$  msec). Long IVRT persisted in the control group through the study ( $p=0.012$ ).

**Conclusion:** Symptoms of hypothyroidism are common in subjects with SH, and L-T4 replacement can improve the cardiac and metabolic derangements.

### Introduction

SH is defined as a serum thyroid stimulating hormone (TSH) above the upper limit of the reference range, with a serum T4 and T3 thyroxine within the reference range. Other causes of a raised TSH such as a past history of thyroid disease and patients on T4 hormone treatment need to be excluded. Although patients with subclinical thyroid disease are usually asymptomatic, but nearly 30% have symptoms or signs of hypothyroidism [1,2].

The prevalence of SH ranges between 4% and 8.5%, although this figure increases with age, and may reach up to 20% in women above 60 years of age. The progression to overt hypothyroidism is approximately 5% per year. The rate of progression is proportional to baseline TSH concentration and higher in individuals with antithyroid antibodies [1,3,4].

There have been studies to attempt to define the nature of association of adverse cardiac events/cardiac dysfunction, effects on lipids, neuropsychiatric symptoms and systemic hypothyroid symptoms [5-9].

Subtle echocardiographic changes have been demonstrated in numerous small studies, however all these studies had significant limitations [7-11]. Resting diastolic dysfunction is usually an early sign of the SH, and it has been clearly shown that it may cause impaired exercise capacity via disturbing the systolic function [12-14].

While small interventional treatment trials assessing the effects of T4 replacement therapy have shown some improvement in serum lipid and cardiac parameters, these are of uncertain significance, and there has not been any randomised study on important clinical endpoints [14-16].

In this prospective study, we evaluated the presence of clinic symptoms and signs of hypothyroidism, serum metabolic parameters and cardiac functions of subclinical hypothyroid subjects who were diagnosed at our outpatient clinic. We also evaluated the efficiency of T4-replacement therapy on these parameters.

### Material and Methods

Consistent with the general acceptance, SH was considered when serum T3 and T4 were in their normal laboratory ranges but sensitive TSH measurement higher than its upper normal limit. Fifty-three patients with SH who were drug naive were enrolled to the study. Randomly, 29 subjects were assigned to the therapy group and given levothyroxine sodium as a replacement dose, and 24 subjects were followed as the control group without any treatment. Medical history, physical examination, body mass index (BMI), symptoms and findings of the subjects were obtained at onset (basal) and the end of the study (at 6 month). In addition to these, 12h-fasting serum laboratory parameters of lipid profile, TSH, fT3, fT4, thyroid auto-antibody

**\*Corresponding author:** Mehtap Evran, Cukurova University Medical Faculty, Department of Internal Medicine, Division of Endocrinology, 01330 Adana, Turkey, Tel: +905327818634; Fax: 00903223386879; E-mail: [mehtap.evran@hotmail.com](mailto:mehtap.evran@hotmail.com)

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(thyroid peroxidase and anti thyroglobulin antibody), homocystein levels were measured. Local ethical committee approved the study.

Cardiological investigations were performed with 24-h Holter ECG (DMS 300-7, Nevada, USA) and transthoracic Doppler echocardiography (ACUSON SEQUOIA C 256) by the same cardiologist. Mean cardiac velocity, atrial and ventricular extra systoles and arrhythmias were investigated. Colour, pulse wave Doppler (PWD), and pulse wave tissue Doppler (PWDDI) were performed. M-mode (mm/s) left ventricular measurements were obtained. Left ventricular ejection fraction (EF) was calculated according to modified Simpson rule. Em degree and Am wave, deceleration time (DT) and IVRT were measured from PWD data of the subjects. Sixteen segments of the myocard PWDDI registrations were obtained by the Tissue Doppler investigation (DDI, 100 mm/s) parasternal long axis and 4 apical and 2 cavity sections. Peak myocardial systolic flow speed (S wave), peak myocardial early diastolic flow speed (E wave) and peak myocardial late diastolic flow speeds (A wave) were measured. Additionally, the ratio of E/A was calculated from the data of PWD and PW DDI.

At the end of the study (at 6 month), both groups were compared with each other for the study parameters.

### Statistical analysis

SPSS version 17.0 package program was used for the statistical investigations. Categorical measurements were expressed as numerical and percentage, and continuous variables, mean and standard deviation (mean ± SD). Chi-square test was used for comparison of the categorical measurements between the groups. For the continual measurements, paired *t*-test (for dependent samples) and *t*-test (for independent samples) and Mann Whitney U test (if needed) were performed. The temporal changes of the continual samples were obtained by subtraction of month 6 samples from initial (basal) samples. Comparements of the groups were performed by *t*-test for dependent groups and Wilcoxon Signed Rank test (when hypothesized median above the hypothesized value). *P* value was considered as 0.05 for all tests.

### Results

Mean age of the subjects (40 female, 13 male) was 44.02 ± 13.9, BMI 29.4 ± 6.4. Systolic blood pressure was 126.5 ± 22.8 mmHg, diastolic blood pressure 78.1 ± 14 mmHg and pulse was 75.9 ± 9.4 per minute.

History of thyroid disease in relatives of the subjects was positive in 22 subjects (41.5%). Twenty three of the subjects did not have any other disease. Twelve had been using antihypertensive medication for primary hypertension.

Symptoms of the subjects: the most remarkable symptoms were weight gain and obesity (n=30; 56.6%); palpitation, constipation (n=27), alopecia (49.1%) and memory problem. At 6 month; those who had obesity were significantly reduced (p=0.037). The number of subjects with constipation and alopecia decreased from 50.9% to 32.1% and 49.1% to 20.8% respectively. Regarding BMI, blood pressure and pulses, no difference was found at 6 month.

Cardiac morphology and functions: In the basal investigation of subjects; sinus rythm was revealed in 39 (73%), sinus bradycardia in 4, sinus tachycardia in 2 subjects and missing of R progression in 4 subjects. In addition, left axis deviation was present in 1, left ventricular hypertrophy voltage criteria in 1, atrial fibrillation in 1 and ventricular extrasystol in 1 subject. At 6 month 24-h Holter ECG examination of all subjects did not show significant difference in the mean cardiac speed (velocity) when compared to baseline measurement. Ejection fraction

by ECO did not show any significant changes at 6 month compared to basal measurements (p=0.43). At onset of the study, mean Em/Am ratio of subjects was found in normal ranges (1.14 ± 0.4, normal >1)

Assessment of thyroid functions according to T4-replacement status:

Table 1 summarizes the thyroid function tests of both groups. When compared to the basal measurements, serum TSH and fT3 levels of the non-treated group were significantly decreased (p=0.005 and p=0.017, respectively), but serum fT4 levels did not change significantly (p=0.29). In subjects with T4-replacement, although there was no significant change in fT3 levels, a significant increase in fT4 levels (p=0.013) and a significant decrease in TSH levels (p=0.00) were found.

Comparing of both groups, serum TSH levels at 6 month were found at the power limit which was relatively in favour of T4-replacement (p=0.053). No significant difference in serum thyroid auto-antibodies was found in both groups.

Assessment of serum lipid parameters according to T4-replacement status:

Basal lipid parameters (LDL, HDL, and triglyceride) of the subjects were within normal ranges, serum Lp (a) was over the normal level (Table 2). In the control group, serum LDL levels increased significantly at 6 month (p=0.01). However, In the T4-replacement group, a non-significant decrease was found in serum LDL levels (p= 0.75). No difference was found in serum HDL, triglyceride and Lp (a) levels in both groups at 6 month.

Assessment of cardiac functions based on T4-replacement status:

Data of 24-h Holter examinations showed no difference in both groups regarding with mean cardiac velocity, the lowest mean cardiac velocity and the highest mean cardiac velocity (at 6 month vs. basal).

Doppler ECO measurements according to the treatment status of subjects are displayed in Table 3. While LVd diameters of subjects without T4-replacement did not show any difference, of those with T4-replacement increased significantly at 6 month (p=0.023). Em degree decreased in both groups at 6 month, however, this decrement was significant in the non-replacement group (p=0.013).

As a result, Em/Am ratio in those without T4 replacement was found to be decreased (p=0005). Em/Am ratio of the subjects with T4-

Variables	Subjects without T4 (n=24)			Subjects with T4 (n=29)		
	1 (basal)	6 month	p	1 (basal)	6 month	p
fT <sub>3</sub> (pg /mL)	3.3 ± 0.08	3.1 ± 0.09	<b>0.017</b>	3.1± 0.09	3.0± 0.08	0.34
fT <sub>4</sub> (ng/DI)	1.06 ± 0.02	1.09 ± 0.04	0.29	1.09± .02	1.17± .03	<b>0.013</b>
TSH (mIU/L)	6.12 ± 0.25	4.9 ± 0.4	<b>0.005</b>	7.2 ± 0.5	4.6± 0.56	<b>0.00</b>
Anti-TPO(U/mL)	179 ± 48	157 ± 47	0.39	203 ± 47	196 ± 45	0.55
AntiTg(U/mL)	563 ± 199	438 ± 180	0.9	491± 191	400± 143	0.86

**Table1:** The changes in thyroid function tests among subjects with T4 and without T4 replacement therapy (1 month (basal) vs. 6 month) (mean ± SEM).

Variables	Subjects without T4 (n=24)			Subjects with T4 (n=29)		
	1 (basal)	6 month	p	1 (basal)	6 month	p
LDL (mg/dl)	98 ± 6.4	108 ± 6.3	<b>0.01</b>	116.5± 6.5	114 ± 5	0.75
HDL (mg/dl)	54 ± 5	53 ± 4.3	0.42	49 ± 2.5	48.5± 2.5	0.5
Triglycerid (mg/dl)	124 ± 8.7	125.4± 11.8	0.72	171 ± 17	149± 13	0.23
Lp(a) (mg/dl)	45.4 ± 8.2	43.3 ± 7.2	0.52	122.6 ± 71	51 ± 9.8	0.93

**Table2:** The changes in serum lipid parameters among subjects with and without T4 replacement therapy (mean ± SEM).

*Variables	Subjects without T4 (n=24)			Subjects with T4 (n=29)		
	1 (basal)	6 month	p	1 (basal)	6 month	P
EF (%)	69.8 ± 1.1	69.5 ± 0.95	0.84	69.5 ± 1.1	68.6 ± 1	0.4
LVd (mm)	45 ± 0.9	45.4 ± 0.9	0.47	46.4 ± 0.9	48.4 ± 0.7	<b>0.023</b>
LVs (mm)	27.4 ± 0.86	28 ± 1.4	0.6	28 ± 0.8	29.3 ± 0.8	0.1
IVSt (mm)	9.1 ± 0.2	9.2 ± 0.3	0.46	10 ± 0.2	9.8 ± 0.2	0.24
PWt (mm)	8.9 ± 0.2	8.9 ± 0.2	0.97	9.4 ± 0.2	9.3 ± 0.18	0.54
Em (cm/sn)	69.5 ± 3.2	61.5 ± 3.3	<b>0.013</b>	66.3 ± 3	61.7 ± 3.4	0.12
Am (cm/sn)	59.5 ± 3.6	59.4 ± 3	0.97	68.5 ± 3.5	66.4 ± 3.2	0.43
Em/Am	1.3 ± 0.1	1.1 ± 0.08	<b>0.005</b>	1.01 ± 0.05	0.94 ± 0.05	0.13
DT (msn)	202.6 ± 19	204.5 ± 11.6	0.9	193 ± 11.5	192 ± 8.5	0.94
IVRT (msn)	116 ± 10	144.5 ± 9.7	<b>0.012</b>	129 ± 8	127 ± 9.5	0.87
S (m/sn)	14 ± 0.6	14.8 ± 0.7	0.25	15 ± 0.6	14.8 ± 0.6	0.87
E (cm/sn)	19.6 ± 1.1	19.7 ± 1	0.8	18 ± 0.9	17.4 ± 0.9	0.44
A (cm/sn)	17 ± 1.1	18 ± 0.7	0.4	19.4 ± 1	20.9 ± 1.3	0.21
E/A	1.3 ± 0.13	1.1 ± 0.09	0.14	0.99 ± 0.06	0.96 ± 0.09	0.33
LAd (mm)	31.6 ± 0.9	33 ± 0.9	<b>0.006</b>	35.5 ± 0.6	36.5 ± 0.7	0.19

\*LVd: Left ventricular end diastolic diameter, LVs: Left ventricular end systolic diameter, EF: Left ventricular ejection fraction, IVSt: Interventricular septum thickness, PWd: Posterior wall thickness, Em-wave: Peak transmitral early diastolic flow speed, Am-wave: Peak transmitral late diastolic flow speed, DT: Deceleration time, IVRT: Isovolumetric relaxation time, S-wave: Peak myocardial systolic flow speed, E-wave: Peak myocardial early diastolic flow speed, A-wave: Peak myocardial late diastolic flow speed, LAd: Left atrium diameter.

**Table 3:** Comparison of echocardiographic measurements (basal vs. 6 month) of the subjects with and without T4 replacement (mean ± SEM).

replacement was found non-significant when compared to basal ratio (p=0.13).

Basal IVRT values of all subjects were found to be increased. IVRT measurements of the non-replacement group persisted to increase at 6 month (p=0.012). IVRT values of the T4-replacement group did not show any difference with respect to basal measurements (p=0.87). LA diameters of the non-replacement group were found to be increased at 6 month (p=0.006).

Comparison of the amount of TSH decrement and IVRT change between the groups were significantly different (p=0,053 and p=0,005, respectively) and higher in the T4-replacement group, however, Em/Am, LVd values and serum LDL-cholesterol, fT3, fT4 were not significantly different (p>0.5).

## Discussion

Although SH has been considered to be an asymptomatic condition, there are a number of studies showing that it may be associated with many symptoms [1,2,17,18]. In this study, the most common symptoms were constipation, weight gain, memory problem, palpitation and alopecia. The frequency of these symptoms were found to be higher than some other studies, but dry skin and hair problem lower than these studies [1-3]. At 6 month, these symptoms were found to be decreased in T4-replacement group. There was no difference in the weight status of two groups at 6 month.

Results of the clinical studies on SH vary, and there have been many controversies among them. Usually, symptoms are nonspecific and related with some factors such as the duration of the disease, the level of thyroid hormone, individual characteristics and age factors [19-21].

Despite the high prevalence of SH in population, there is no consensus about T4 replacement. The presumed advantages of replacement are considered on serum lipid profile, cardiovascular system and prevention of the development of clinical hypothyroidism and goiter (if present). In addition, a clinical improvement on some

subjective symptoms might be achieved [22].

According to a meta-analysis, it was suggested that those who had persistent serum TSH level greater than 4.0 mIU/L, associated with high thyroid autoantibodies should be treated [22]. However, in an another meta-analysis, it has been suggested that periodic follow up with three months intervals was recommended to the patients with serum TSH level between 4.5 and 10 mIU/L and those with hypothyroidism symptoms should be treated with low dose levothyroxine and if treatment improves the symptoms, replacement should be continued [3]. Despite these data, there is still not clear evidence whether early T4 replacement therapy is useful for the subclinical hypothyroid subjects or not [23-25].

TSH levels of our subjects were between 4.2 and 10 mIU/L (normal upper limit: 4.2 mIU/L). After 6 months, TSH levels of both groups were significantly reduced. However, serum TSH, fT3, and fT4 levels of the treated group were found to be more close to the normal ranges. As a result, T4-replacement could be suggested as useful for subclinical hypothyroid subjects.

Serum TPO and Tg antibodies of our subjects were higher than normal ranges. This implies that autoimmunity is one of the major underlying causes of SH in our subjects. Therefore, we suggest that thyroid antibodies can be measurable to predict the development of SH. Because, it is well known that progression of SH to clinical hypothyroidism is higher in subjects with positive thyroid antibody (4.3% vs. 2.6%) [3,26].

It is also well known that serum lipid abnormality is prevalent in clinical hypothyroidism, and it is considered to cause cardiovascular disorders [27]. Furthermore, it has been reported that SH is associated with high serum total cholesterol and LDL levels and low HDL which could increase the atherosclerosis risk [1,5,27-33]. Serum lipid profiles of our subjects were consistent with these studies. Likewise, serum Lp (a) levels were found to be high as reported by Caraccio et al. [31] This finding could be related with SH and/or genetic characteristics of the subjects.

Another debated issue on SH is the influence of replacement therapy on serum cholesterol level [24,32,33]. A placebo controlled study by Meier et al. [24], showed that levothyroxin replacement significantly decreased the serum total and LDL-cholesterol. In a study by Danese et al. [5], they reported that a decrease in serum LDL cholesterol but no significant change in serum HDL and triglyceride levels. In our study, serum LDL levels of the non-treated group revealed a significant increase (nearly 10 mg/dL) at 6 month, but in the T4-replacement group, serum LDL-cholesterols were minimally reduced. Therefore, our study results also support T-4 replacement in SH. In addition, we also found a non-significant reduction in serum triglyceride and Lp (a) levels in the replacement group.

The studies on SH and cardiovascular system are also controversial. According to the certain studies, SH is harmful to cardiovascular system, but there has not been enough controlled study to reveal this issue [5,34]. In certain studies, especially in the resting period, mean cardiac rate was found to be normal but after levothyroxine therapy, it was increased [32,35,36]. In our study, we also found normal mean cardiac speed but following levothyroxine replacement, did not observe any significant change in mean cardiac speed.

In another study on SH and its cardiac impacts, diastolic cardiac dysfunction in the resting period and systolic dysfunction in the exercise period and a reduced exercise capacity were reported [12,13].



In another study consisting of 26 subclinical hypothyroid subjects by Biondi et al. [10] using Doppler echocardiography, they reported no change in the left ventricular structure and systolic function, but they found an increase in Em/Am rate and markedly prolonged IVRT disclosing diastolic parameters. In these subjects, they found significant improvement in the diastolic dysfunctional parameters following the 6 months of T-4 replacement.

In a meta-analysis by Villar et al. [25], including 350 subjects with SH at a 6 to 14 month follow up period, they reported that levothyroxine replacement made an improvement in clinical symptoms and lipid parameters but, did not affect the cardiovascular morbidity (MI and stroke) and mortality. But, there has not been yet randomized controlled study on levothyroxine replacement therapy and its efficiency on cardiovascular morbidity and mortality.

Regarding our study, 6 months follow up period is not long enough to evaluate cardiac morbidity and mortality, on the other hand, we found significant disturbances in the cardiac functions, and these disturbances showed a progression in those without T4-replacement. EF measurements of our subjects were found to be normal like the results of the study of Foldes et al. But the disadvantage of our study is that there is no euthyroid control group. And we obtained no change in EF measurement after T-4 replacement. We also found normal Em/Am ratio in our subjects. However, IVRT values of all subjects were found to be prolonged similar to the reported studies. Moreover, it persisted to be prolonged in the non-replacement group during the 6 months period.

Em degree of all our subjects showed a decrease at 6 month and especially in the non replacement group, Em/Am ratio was significantly reduced. In other words, two important parameters which show the left ventricular diastolic function were found to be detrimentally influenced by SH.

Left atrial diameters also were found to be significantly enlarged in both groups. But this increase was significantly higher in the non-replacement group in comparison to the replacement group. Although, this finding may imply systolic deterioration, our S wave measurements which show the peak myocardial flow speed were found in normal ranges and no difference was found with T4-replacement.

In conclusion, subclinical hypothyroid subjects can be encountered not only with certain symptoms found in the clinical hypothyroidism but also have hyperlipidemia and important disturbances in the echocardiography parameters. Levothyroxine replacement therapy seems to be beneficial for clinical symptoms, serum lipid parameters and especially left diastolic cardiac function. But further controlled randomized studies are needed especially for the cardiac endpoints.

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