Original Article

# Efficacy of Levothyroxine Therapy on Diastolic Dysfunction in Patients with Subclinical Hypothyroidism

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## Abstract

**Background:** Hypothyroidism is a cause of left ventricular diastolic dysfunction especially in cases with positive history of coronary artery disease. It is suggested that cardiac dysfunction may be improved with thyroxin replacement therapy. However, it is controversial. Hence, in this study the efficacy of levothyroxine therapy on diastolic dysfunction in patients with subclinical hypothyroidism was assessed.

**Materials and Methods:** In this, randomized clinical trial 40 consecutive patients with subclinical hypothyroidism attending to Loghman Hospital in 2018 for the treatment were enrolled. The treatment was 25-50 microgram per day of levothyroxine for one year. During this period, the patients were followed up with visit or phone call with a monthly manner. The echocardiography indices were rechecked after one year beside the thyroid tests by initial lab and operators.

**Results:** The mean BMI was significantly decreased (P=0.001). The T3 and TSH were significantly differed but The T4 had no significant alteration (P>0.05). Among the echocardiographic indices the MV.E, MV.A to MV. E ratio, EF, E′ septal, E′ lateral had significant increase and the MV.A and PV. Adur had significant reduction. After intervention among 40 patients, there were 17 cases with normal diastolic function. The BMI, MV. A, PV Adur, E′ Septal, E′ Lateral, and E to E′ ratio showed significant correlation.

**Conclusion:** Totally, according to the obtained results, it is concluded that diastolic dysfunction as a common problem in patients with subclinical hypothyroidism may be treated with administration of levothyroxine. In addition, screening for diastolic dysfunction in patients with subclinical hypothyroidism is recommended to decrease the burden of problem.

**Keywords:** Diastolic dysfunction, Subclinical hypothyroidism, Treatment

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## Introduction

Subclinical hypothyroidism is the conditions characterized with increased level dr_rgholami of thyroid stimulating hormone (TSH) despite normal serum level of free thyroxin. The serum level of TSH should be measured in cases with normal thyroxin levels suspected to have subclinical hypothyroidism.

Prevalence of hypothyroidism ranges from three to eight percent in general population. The prevalence increase with age and also it is more common among female subjects[1-3]. There are some debates about treatment of cases with TSH levels less than 10 mu/ml[2,5]. Thyroxin replacement therapy would have no effect on improvement of survival or reduction of cardiovascular disorders. But it may result in improved left ventricular function and some serum lipid parameters[2-5]. Screening strategies are initiated at 35 years and would be continued each five years. It has been suggested that screening would be more useful in women older than 50 years. Also it is important to screen and treat the pregnant women to decreased adverse fetal effects[1-7]. Also nearly 2-5 percent of cases with sub-clinical hypothyroidism would develop annually overt hypothyroidism subsequently[1-3]. However the lipid abnormalities may improve after thyroxin replacement therapy the improvement in endothelial function and insulin resistance after replacement therapy has been also suggested[1-5].

The cardiac function and contractility are mediated by thyroid hormones by adenine cyclase enzyme resulting in increased heart rate[1-5]. However the other side effects such as myocardial infarction, aortic calcification, and cardiac dysfunctions are controversial[5-10]. Hypothyroidism is a cause of left ventricular diastolic dysfunction especially in cases with positive history of coronary artery disease[11-14]. It is suggested that cardiac dysfunction may be improved with thyroxin replacement therapy[15-18]. But it is controversial. Hence in this study the efficacy of levothyroxine therapy on diastolic dysfunction in patients with subclinical hypothyroidism was assessed.

## Methods

In this randomized clinical trial 40 consecutive patients with subclinical hypothyroidism (according to two lab tests with three-month interval) attending to Loghman Hospital in 2018 for the treatment were enrolled. Exclusion criteria were hypertension, hyperlipidemia, diabetes mellitus, ischemic heart disease, renal failure, and smoking. The informed consent form was received from all patients and the study was approved by local ethical committee with approcal ode of Ir.sbm.msp.rec.1395890. Helsinki Declaration was respected across the study.

All lab studies were done in single lab. The patients respecting all inclusion criteria were introduced to cardiologist and left ventricular diastolic function indices were determined by Echocardiography scale. Totally 130 patients were included among them finally 40 subjects were enrolled in final analysis. The treatment was 25-50 microgram per day of levothyroxine for one year. During this period the patients were followed up with visit or phone call with a monthly manner. The echocardiography indices were rechecked after one year beside the thyroid tests by initial lab and operators. Also blinding was done for echocardiography operator.

Data analysis was done by SPSS version 22.0 software among 40 patients including 20 male and 20 female subjects. The utilized tests were independent-sample-T and linear regression assays. The P values less than 0.05 were considered statistically significant.

## Results

The study was carried out among 20 men and 20 women with mean age of 45.9 ± 13.1 years. The baseline and after-one year results are demonstrated and compared in Table 1. As seen in this Table the mean BMI was significantly decreased (P=0.001).

The T3 and TSH were significantly differed but The T4 had no significant alteration (P > 0.05). Among the echocardiographic indices the MV.E, MV.A to MV. E ratio, EF, E′ septal, E′ lateral had significant increase and the MV.A and PV.Adur had significant reduction. After intervention among 40 patients there were 17 cases with normal diastolic function. The BMI, MV. A, PV Adur, E′ Septal, E′ Lateral, and E to E′ ratio showed significant correlation (Table 2).

## Discussion

Subclinical hypothyroidism is accompanied with left ventricular remodeling that is established by two-dimensional and three-dimensional echocardiography that reveals diastolic dysfunction[19-23]. In addition, it would result in increased rate of coronary artery disease and dyslipidemia. We found that levothyroxine therapy decreased diastolic dysfunction in cases with subclinical hypothyroidism[20-22]. According to new

**Table 1:** Baseline and after one year results.

| Variable | Mean | Std. Deviation | Value |
|---|---|---|---|
| **BMI before intervention** | 25.9205 | 3.15 | 0.000 |
| **BMI after intervention** | 25.2026 | 2.94 | |
| **TSH before intervention** | 8.5800 | 1.99 | 0.000 |
| **TSH after intervention** | 1.4925 | 0.70 | |
| **T4 before intervention** | 6.4775 | 1.35 | 0.055* |
| **T4 after intervention** | 7.1700 | 1.62 | |
| **T3 before intervention** | 108.77 | 18.67 | 0.0001 |
| **T3 after intervention** | 144.1750 | 45.28 | |
| **MV.E before intervention** | 0.5848 | 0.084 | 0.0019 |
| **MV.E after intervention** | 0.6710 | 0.16 | |
| **MV.A before intervention** | 0.7423 | 0.08 | 0.003 |
| **MV.A after intervention** | 0.6873 | 0.10 | |
| **MV.E.to.A before intervention** | 0.7965 | 0.13 | 0.003* |
| **MV.E.to.A. after intervention** | 1.0145 | 0.33 | |
| **PV.Adur before intervention** | 124.6000 | 36.00 | 0.763* |
| **PV.Adur after intervention** | 117.2750 | 20.48 | |
| **EF before intervention** | 56.0000 | 2.58 | 0.230 |
| **EF after intervention** | 57.0500 | 0.31 | |
| **E′ Septal before intervention** | 0.0893 | 0.09 | 0.001* |
| **E′ Septal after intervention** | 0.1010 | 0.09 | |
| **E' Lateral before intervention** | 0.1170 | 0.070 | 0.040* |
| **E′Lateral after intervention** | 0.1340 | 0.06 | |
| **E.to.E′ before intervention** | 7.9486 | 1.57 | 0.996 |
| **E.to.E′ after intervention** | 7.9500 | 1.313 | |

guidelines, the low-dose levothyroxine should be initiated in the patients with subclinical hypothyroidism[23-30]. In addition, screening by echocardiography in such patients is recommended.

Regarding the increasing trend of hypothyroidism and increased related mortality and morbidity among patients especially due to heart failure further care for them is crucial. In our study, the mean age was in fourth life decade. The study by Yazici et al[30] showed that patients were aging from 38 to 40 years. In addition, we found that majority of patients had high BMI but the levothyroxine therapy resulted in significant decrease in BMI. However, the narrow age range in current study could not miss the significant alterations. The study by Franzonia et al[27] demonstrated that BMI was same across the patients with subclinical hypothyroidism and euthyroid subjects.

In our study, it was understood that levothyroxine use results in significant reduction in TSH level resulting in a mean in normal age in post-treatment stage. This matter was also seen in the study by Yazici et al[30] but after six months of treatment. However, we had only two measurements and it is not clear that in which month the TSH was decreased initially to the normal serum level. After intervention the echocardiographic indices of MV.E, MV.A to MV. E ratio, EF, E′ septal, E′ lateral had significant increase and the MV.A and PV.Adur had significant reduction. In the other instances, there was no significant alteration. Franzonia et al[27] revealed that Em and Em/Am ratio were significantly increased and the other indices had no significant alteration. For further understanding about the clinical relevance of these alterations in echocardiographic factors, further studies would be useful.

**Table 2:** Correlation of before and after factors with thyroxin treatment.

| Before and after intervention | Correlation | P Value |
|---|---|---|
| **BMI** | 0.956 | 0.000 |
| **TSH** | -0.077 | 0.639 |
| **T4** | 0.043 | 0.792 |
| **T3** | -0.019 | 0.906 |
| **MV.E** | 0.247 | 0.125 |
| **MV.A** | 0.361 | 0.022 |
| **MV E to A ratio** | 0.170 | 0.296 |
| **PV Adur** | 0.513 | 0.001 |
| **E′ Septal** | 0.978 | 0.000 |
| **E′ Lateral** | 0.962 | 0.000 |
| **E to E′ ratio** | 0.481 | 0.003 |

Erkan et al[26] demonstrated that myocardial function had no significant alteration after intervention with levothyroxine but the mitral annular E velocity had significant improvement. It is in congruence relatively with our study. Improvement in diastolic function also is demonstrated with consideration of a healthy control group[15]. As shown in some studies[30] the diastolic dysfunction is reversible in patients with subclinical hypothyroidism after levothyroxine replacement therapy. The correlation between the clinical and echocardiographic factors, in our study, demonstrates the importance of interventions according to the other contributing factors in these patients.

## Conclusion

Totally, according to the obtained results, it is concluded that diastolic dysfunction as a common problem in patients with subclinical hypothyroidism may be treated with administration of levothyroxine. In addition, screening for diastolic dysfunction in patients with subclinical hypothyroidism is recommended to decrease the burden of problem. However further studies with larger sample size and multi-center samplings are required to attain results that are more definite in this era.

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