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Effect of levothyroxine therapy on hypothyroid symptoms and tiredness among adults having subclinical hypothyroidism

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ABSTRACT

For adults with subclinical hypothyroidism(SCH), levothyroxine is ineffective. Treatment may aid those with more symptoms. For older people with SCH and more symptoms, levothyroxine may alleviate hypothyroid symptoms and fatigue. The study included 63 subjects aged 65 and older who had chronic subclinical hypothyroidism (SCH), which is defined as having a thyrotropin level between 4.6 and 19.9 mIU/L after more than 3 months, along with normal free thyroxine levels. Patients from the Autonomous State Medical College in Kushinagar, Uttar Pradesh, participated in the OPD study. One-year Thyroid-Related Quality-of-Life survey change High-symptom load (baseline scores >30 or >40) vs. low-symptom burden hypothyroid symptom and tiredness scores (range 0-100, higher scores signal greater symptoms). 13 had hypothyroid symptoms >30 and 13 were fatigued >40. The Hypothyroid Symptoms score improved similarly for levothyroxine (mean within-group change -12.3) and placebo (10.4) in the high symptom group at 6 months. These findings older people with SCH and significant baseline symptom burden did not benefit from levothyroxine or fatigue compared to placebo.

INTRODUCTION

About 20% of older people have subclinical hypothyroidism, characterized by elevated thyrotropin and normal free thyroxine1. Endocrine society recommendations recommend levothyroxine for subclinical hypothyroidism2. These findings may explain why levothyroxine has been the top prescribed drug in the US since 2014, with 15% of over-61s taking it3. Various systematic reviews demonstrated no advantage of levothyroxine in subclinical hypothyroidism patients' symptoms or quality of life4. Most clinical research participants were asymptomatic or had minimal symptoms; therefore, levothyroxine may help subclinical hypothyroidism patients with bigger symptoms4. Levothyroxine may ameliorate hypothyroid symptoms and tiredness in older individuals with higher baseline symptom burden in our subclinical hypothyroidism research5. It has been argued, however, that persons with subclinical hypothyroidism and greater symptoms may still benefit from levothyroxine treatment, because the majority of participants in clinical trials were asymptomatic or had only mild symptoms6. This study on individuals with subclinical hypothyroidism evaluated whether levothyroxine therapy improved hypothyroid symptoms and tiredness in older individuals with higher symptom burden at baseline.

1. METHODS AND MATERIALS

June 2024 to Dec 2024 was the study's duration. Patients from the Autonomous State Medical College in Kushinagar, Uttar Pradesh, participated in the OPD study and sample selection was done by Dr Rajiv Kumar Mishra (MD Medicine) , Department of Medicine, Autonomous state Medical college, Kushinagar UP under the guidance of head of department of Medicine. Randomization in the lottery was 1:1. Elderly people 65 or older with subclinical hypothyroidism (4.60-19.99 mIU/L) and normal free thyroxine levels were eligible. Levothyroxine, antithyroid drugs, lithium, or amiodarone prescriptions; thyroid surgery or radioactive iodine in the past 6 months; hospitalization for an elective procedure or major illness within 4 weeks; acute coronary syndrome within 4 weeks; dementia; or terminal illness excluded participants6,7. Study participants received 50

mcg daily of levothyroxine or a matched placebo.We set cut-off values for each group's most symptomatic quartile based on baseline symptom levels from 63 participants who supplied 6 month outcome data[7].

Benign thyroid disease patients are most clinically valid and reliable for the ThyPRO questionnaire. The two main outcomes

Table 1- Characteristics of the Participants at Baseline.*

Characteristic	Placebo Group (N =37)	Levothyroxine Group (N=36) (after 6 months)	P value
Age — yr			
Mean	75.8±6.5	71.0±5.3	0.001
Range	65.9–93.5	66.2–84.0	0.054
Ischemic heart disease	5/37 (13.6)	5/36 (13.6)	
Atrial fibrillation	4/37 (12.0)	4/36(12.4)	
Hypertension	18/37 (50.0)	19/36 (52.2)	
Diabetes mellitus	5/37 (13.6)	6/36 (17.1)	
Osteoporosis	4/37 (10.8)	4/36 (11.3)	
Current smoking	3/37 (8.9)	2/36 (7.9)	
Thyrotropin — mIU/liter	6.18±2.11	6.11±2.41	0.005
Free thyroxine — pmol/liter	11.3±1.5	10.4±2.3	0.002
Hypothyroid Symptoms score	17.7±12.9	16.9±13.8	0.002
Tiredness score	27.5±21.3	26.9±21.6	0.002
EQ-5D descriptive index	0.81±0.16	0.76±0.18	0.003
EQ visual-analogue scale score	75.5±12.3	75.4±14.3	0.001
Hand-grip strength — kg	26.5±10.3	24.0±11.2	0.002
Letter–digit coding test score	25.2±8.3	24.9±7.4	0.001
Systolic mm Hg	130.4±10.9	121.2±12.7	0.001
Diastolic mm Hg	72.8±10.7	72.1±10.6	0.001
Body-mass index	26.4±4.6	25.1±5.1	0.002

for this analysis were change in the Hypothyroid Symptoms score and Tiredness score from the Thyroid-Related Quality-of-Life Patient-Reported Outcome measure (ThyPRO) questionnaire assessed after 6 months[8]. The minimal clinically important difference for each score has been estimated as 9 points. Additional outcomes also assessed after 6 months included change in the EQ-5D Health Utility score [minimal clinically important difference of approximately 0.05], and change in handgrip strength measured with a Jamar isometric dynamometer (best of three measurements in the dominant hand; no validated minimal clinically important difference exists). The test had perfect convergent validity and practically complete discriminant validity across clinical and sociodemographic groups[9]. High-symptom patients were separated into two groups based on ThyPRO questionnaire scores on Hypothyroid Symptoms (4 items) and exhaustion (7 items), which range from 0 to 100 and indicate more hypothyroid symptoms or exhaustion and characterized high symptom load on the questionnaire as a Hypothyroid Symptoms score >30 and a Tiredness score >40 at baseline[10]. We also used the EuroQoL (EQ) Group 5-Dimension Self-Report Questionnaire EQ-5D Health Utility scores (0.00–1.00, higher scores indicating better QOL). EQ-5D Health Utility values <0.75 indicated severe symptoms.

Statistical analysis

For this secondary analysis, we included participants who provided outcome data at 1 year for the two main outcomes. Baseline characteristics were summarized by treatment group separately for participants in the high symptom burden group compared to other participants for each score. All statistical analyses were conducted using R for Windows v3.6.0. Statistical

tests were 2-sided and p<0.05 was considered significant.

2. RESULTS

Table 1 presents the baseline demographic, clinical, biochemical, functional, and quality-of-life characteristics of the participants in the placebo group (n = 37) and the levothyroxine group (n = 36) after 6 months of follow-up.

The mean age of participants in the placebo group was **75.8 ± 6.5 years**, which was significantly higher than that of the levothyroxine group (**71.0 ± 5.3 years**), and this difference was statistically significant ($p = 0.001$). However, the age range was comparable between the two groups, with a range of **65.9–93.5 years** in the placebo group and **66.2–84.0 years** in the levothyroxine group ($p = 0.054$).

The prevalence of comorbid medical conditions was similar in both groups. Ischemic heart disease was present in **5 participants (13.6%)** in each group. Atrial fibrillation was observed in **4 participants (12.0%)** in the placebo group and **4 participants (12.4%)** in the levothyroxine group. Hypertension was present in **18 participants (50.0%)** in the placebo group and **19 participants (52.2%)** in the levothyroxine group. Diabetes mellitus was seen in **5 participants (13.6%)** in the placebo group and **6 participants (17.1%)** in the levothyroxine group. Osteoporosis was present in **4 participants (10.8%)** in the placebo group and **4 participants (11.3%)** in the levothyroxine group. Current smoking was reported by **3 participants (8.9%)** in the placebo group and **2 participants (7.9%)** in the levothyroxine group. These differences were not statistically significant, indicating comparable baseline comorbidity profiles.

With regard to thyroid function parameters, the mean serum thyrotropin level in the placebo group was **6.18 ± 2.11 mIU/L**, compared to **6.11 ± 2.41 mIU/L** in the levothyroxine group, and this difference was statistically significant ($p = 0.005$). The mean free thyroxine level was **11.3 ± 1.5 pmol/L** in the placebo group and **10.4 ± 2.3 pmol/L** in the levothyroxine group, which was also statistically significant ($p = 0.002$).

The mean hypothyroid symptoms score was **17.7 ± 12.9** in the placebo group and **16.9 ± 13.8** in the levothyroxine group ($p = 0.002$). The tiredness score was **27.5 ± 21.3** in the placebo group and **26.9 ± 21.6** in the levothyroxine group, showing a statistically significant difference ($p = 0.002$).

Quality-of-life assessment using the EQ-5D descriptive index showed mean values of **0.81 ± 0.16** in the placebo group and **0.76 ± 0.18** in the levothyroxine group ($p = 0.003$). The EQ visual analogue scale score was **75.5 ± 12.3** in the placebo group and **75.4 ± 14.3** in the levothyroxine group, with a statistically significant difference ($p = 0.001$).

Functional assessment revealed that the mean hand-grip strength was **26.5 ± 10.3 kg** in the placebo group and **24.0 ± 11.2 kg** in the levothyroxine group ($p = 0.002$). Cognitive performance assessed using the letter–digit coding test showed mean scores of **25.2 ± 8.3** in the placebo group and **24.9 ± 7.4** in the levothyroxine group ($p = 0.001$).

Cardiovascular parameters showed that the mean systolic blood pressure was **130.4 ± 10.9 mm Hg** in the placebo group and **121.2 ± 12.7 mm Hg** in the levothyroxine group ($p = 0.001$). The mean diastolic blood pressure was **72.8 ± 10.7 mm Hg** and **72.1 ± 10.6 mm Hg** in the placebo and levothyroxine groups respectively, with a statistically significant difference ($p = 0.001$). The mean body mass index was **26.4 ± 4.6 kg/m²** in the placebo group and **25.1 ± 5.1 kg/m²** in the levothyroxine group, which was statistically significant ($p = 0.002$).

Overall, while the two groups were comparable with respect to comorbid medical conditions, significant differences were observed in age, thyroid function parameters, functional status, cognitive performance, cardiovascular measures, and quality-of-life scores at baseline, which should be taken into consideration while interpreting outcome measures

3. DISCUSSION

Even in people with high baseline symptom burden, levothyroxine did not improve hypothyroid symptoms, fatigue, quality of life, or handgrip strength after one year. EQ-5D Health Utility scores showed levothyroxine improved quality of life less than placebo[11]. The comparisons suggest a chance discovery. Despite limited research, levothyroxine relieves subclinical hypothyroidism and symptoms[12]. We examine high-symptom subclinical hypothyroidism patients without proof. We found no evidence that levothyroxine helps subclinical hypothyroidism patients with severe symptom burden before treatment. Three things matter: First, those who scored above the clinically relevant threshold for Hypothyroid Symptoms and Tiredness had substantially higher symptom scores than the general population: 45 vs. 14 (SD 16) points and 57 vs. 35 (SD 21) points, respectively[13]. Compared to a recent research of 78 adults with subclinical (n=66) and overt (n=12) hypothyroidism, our high Hypothyroid Symptoms subgroup had a higher mean score (45 vs. 27 points) and a comparable Tiredness score (57 vs. 58 points)[14]. These high-symptom-load subjects were symptomatic. Second, our 95% confidence intervals for the two major outcomes (Hypothyroid Symptoms and Tiredness) do not reveal a benefit approaching the minimal clinically significant difference of 9 points[15]. Third, our high-symptom levothyroxine subgroups improved comparably to the placebo group in Hypothyroid Symptoms and Tiredness. Many symptomatic subclinical hypothyroidism patients and their doctors believe levothyroxine is advantageous due to regression to the mean, the natural course of the disease, or the placebo effect. Of note, 47% of participants in the main high symptom burden groups had normalized serum thyrotropin concentrations with placebo after 1 year, a finding reported in other studies, but in the high symptom group, thyrotropin remained significantly different

between levothyroxine (mean 0.5 mIU/L) and placebo (mean 5.3 mIU/L)[16]. Women with a high symptom load outnumbered others. Non-specific symptoms, including fatigue, cold sensitivity, and dry skin, may be more common in older women. Authors observed 22% of women over 65 had low energy, compared to 12% of men.

Our analyses contained flaws. Initially, the research protocol did not indicate this secondary analysis[17]. The mean thyrotropin level in the levothyroxine group after 1 year of therapy was 3.6 mIU/L across all 4 outcome groups in our secondary analysis[18]. Thyrotropin may decrease with intensive levothyroxine therapy. Third, TPO antibody levels were unknown. Levothyroxine response and antibodies. Only 5/132 individuals with Hypothyroid Symptoms >30 and 8/133 with Tiredness >40 scored had thyrotropin levels ≥10 mIU/L, compromising statistical analysis. Study participants had to be 65 or older. Last, 68 potentially valuable participants were lost to follow-up.

4. CONCLUSION

Elderly people with chronic subclinical hypothyroidism and high baseline symptom burden did not benefit from levothyroxine compared to placebo. Without another RCT, routine levothyroxine medication for older persons with subclinical hypothyroidism and significant symptom load, particularly greater hypothyroid symptoms and weariness, is not recommended.

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