RESEARCH ARTICLE

# Normalisation of serum TSH doesn't represent true euthyroidism for patients on levothyroxine treatment

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## Abstract

**Objective:** To evaluate whether normalisation of serum thyroid-stimulating hormonelevels with levothyroxine is related with metabolic parameters and psychologic wellbeing.

**Method:** The observational, case-control study was conducted from to May to July 2019 in the outpatient thyroid clinics of Fatih Sultan Mehmet Education and Research Hospital, Istanbul, Turkey, and comprised of hypothyroid patients in the euthyroid state with levothyroxine treatment and euthyroid controls. Psychological wellbeing was assessed using the General Health Questionnaire-12, and metabolic parameters with lipid levels and body composition were analysed for both the groups. Data was analysed using SPSS 25.

**Results:** Of the 159 subjects, 110(69%) were cases with a mean age of 50.1±11.7 years, and 49(31%) were controls with a mean age of 47.3±15.2 years. There was no significant difference related to thyroid-stimulating hormone levels between the groups (p=0.191). Free throxine levels were significantly higher in the cases, while free triiodothyroinine levels were higher in the controls (p<0.001). Total cholesterol and triglycerides levels were significantly higher in the cases than the controls (p<0.05). The cases had lower basal metabolic rate and fat free mass than the controls, but the difference was not significant (p>0.05). The cases scored higher in terms of wellbeing than the controls, but the difference was not significant (p>0.05).

**Conclusion:** Thyroid hormone replacement needs to be adjusted to provide a satisfactory treatment for hypothyroid patients with normal thyroid-stimulating hormone levels who remain clinically and biochemically asymptomatic. In symptomatic patients, peripheral parameters of hypothyroidism, such as lipid levels, physiological symptoms and quality of life, might be useful in determining the levothyroxine dose and bringing the thyroid-stimulating hormone level within the normal range.

**Keywords:** Hypothyroidism, Euthyroidism, Levothyroxine replacement, Low triiodothyronine. (JPMA 72: 827; 2022)

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## Introduction

The current treatment for hypothyroidism is levothyroxine (LT4) monotherapy.[1] LT4 is a synthetic thyroid hormone administered orally to achieve normal serum thyroid-stimulating hormone (TSH) levels as well as to ensure physical and mental wellbeing. The thyroid gland produces thyroxine (T4) and active thyroid hormone triiodothyronine (T3) which is mainly (80%) synthesized by peripheral conversion of T4 by 5′-deiodinase. Hence, L-T4 monotherapy is accepted as the preferred hormone replacement mode in hypothyroidism.

However, many patients under LT4 supplementation and with serum TSH in the reference range have persistent complaints, such as cognitive dysfunction, fatigue, and impaired psychological wellbeing.[2-4] These observations point out that even if serum free T4 (FT4) levels reach normal in patients receiving LT4, serum T3 levels remain still low. A study explained that in athyrotic patients in whom T3 secretion is insufficient, T4-T3 conversion may not be enough to reach normal T3 levels.[5] Another possible reason is that the genetic variations of deiodinases and thyroid hormone transporters cause variable amounts of intracellular T3 levels and T3/T4 ratio in different tissues.[6]

Over the last decade, screening, diagnosis and treatment of hypothyroidism is focussed on laboratory-based approach according to sensitive TSH measurements. As in thyroid haemostasis, T3, T4 and TSH involve inter-individual differences, it is hard to simplify thyroid pathologies on a single parameter.[7] Lipid parameters, psychological assessment and basal metabolic rate (BMR) are screened to evaluate euthyroidism rather than serum TSH levels.[3]

However, the debate is still on about what true hypothyroidism really is or whether fixed-dose LT4 therapy is appropriate for treatment goals. Some trials suggested a combination therapy with liothyronine (LT3) in symptomatic patients treated with LT4 therapy, but

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failed to show any advantages of LT3, and only recommended it for selected cases.[8]

The opinion is that LT4 treatment and serum TSH within normal range might not be enough to represent euthyroidism. The current study was planned to determine whether normalisation of serum TSH levels with LT4 is related with metabolic and psychologic wellbeing.

## Patients and Methods

The observational, case-control study was conducted from May to July 2019 in the outpatient thyroid clinics of Fatih Sultan Mehmet Education and Research Hospital, Istanbul, Turkey. After approval from the institutional ethics review board, the sample size was calculated using G-Power 3.1 calculator.[9] The number of samples determined for effect size: 0.924, standard deviation 11.9 and N2/N1 =0,33 was a total of 70 (minimum sample size n=53 group 1; minimum n= 17 group 2) with 94% power and $\alpha$: 0.05.[10]

We enrolled hypothyroid patients receiving LT4 therapy and euthyroid controls. In the LT4-treated group, patients over the age of 18, receiving LT4 for at least one year and having euthyroid status constituted the patient group, while the control group consisted of age and gender-matched euthyroid individuals.

Participants with pregnancy, lactation, neurological or psychiatric disorders and other endocrine diseases, renal failure, cancer, acute medical condition, and patients taking beta-blockers, antidepressants and statins were excluded. Patients who received LT4 prior to blood sampling were also excluded to avoid falsely elevated FT4 levels.

After taking written informed consent, demographic data including, age, gender, weight, body mass index (BMI), comorbidities and medications was recorded for each subject. Medication list was obtained from the electronic records. TSH, FT4, FT3, fasting plasma glucose (FPG), glycated haemoglobin (HbA1c), creatinine, total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglyceride (TG), C-reactive protein (CRP), ferritin, haematocrit (Hct) and haemoglobin (Hb) levels were obtained from the patient records. Serum TSH analysis was measured by chemiluminescence (CL) immunoassay method (Architect i2000, Abbott Laboratories) with functional sensitivity 0.005 mIU/L. Serum TSH level for euthyroid state was defined as 0.5-4.2mIU/L.

Tanita's bioelectrical impedance analysis (BIA) was used to determine BMR, fat mass percentiles (FM), fat-free mass (FFM) and total body water (TBW). Each participant was warned not to take excessive food/fluid, and urinated before the measurements were taken. The measurements were made early in the morning after a 10-12h fasting.

To assess the mental health and psychological wellbeing, the General Health Questionnaire-12 (GHQ-12), a self-administered screening tool associated with global quality of life (QOL), was used.[11] GHQ-12 is a reliable screening tool in different populations, including the Turkish population.[12] The questionnaire consists of 12 items with four responses scored on a 0-3 Likert scale ranging from 'more so than usual' to 'much less than usual'. The total score range is 0-36, with higher score demonstrating worse mental status.

Data were analysed using SPSS 25. The findings were expressed as frequencies and percentages, mean ± standard deviation and median with interquartile range (IQR)). Normal distribution of data was assessed using the Kolmogorov Smirnov test. Student's t-test was used to compare normally distributed parameters between two groups, and Mann-Whitney U test was used for comparisons of parameters not showing normal distribution between two groups. Bivariate correlation analyses were performed using the Pearson correlation test in case of normally distributed data, or Spearman test for cases without normal distribution. Chi-square test was used to compare qualitative data. $P<0.05$ was considered statistically significant.

## Results

Of the 159 subjects, 110(69%) were cases with a mean age of 50.1±11.7 years, and 49(31%) were controls with a mean age of 47.3±15.2 years. There were no significant differences between the two groups (Table-1).

There was no significant difference related to TSH levels between the groups (p=0.191), while FT4 levels were significantly higher in the cases, and FT3 levels were higher in the controls (p<0.001) (Table-2).

TC and TG levels were significantly higher in the cases than the controls (p<0.05). The cases had lower BMR and FFM than the controls, but the difference was not significant (p>0.05). The cases scored higher in terms of wellbeing than the controls, but the difference was not significant (p>0.05) (Table-3).

Overall, there was no significant correlation of GHQ-12 with TSH, FT4 and FT3 (p>0.05).

**Table-1:** Characteristics of the LT4-treated group 1 and controls group 2.

| | Group 1 (n:110) | Group 2 (49) | P value |
|---|---|---|---|
| **Age (year)**** | | | |
| Mean±SD | 50,1 ±11,7 | 47,3 ±15,2 | 0,68 |
| Median (IQR) | 52 (25-61) | 51(35-59) | |
| **Gender ***** | | | |
| Male | 13 (% 11,8) | 8 (%16,3) | 0,46 |
| Female | 97(%88,2) | 41(%83,7) | |
| **BMI (kg/m2)*** | | | |
| Mean±SD | 29,1 ±5,4 | 29,2 ±5,89 | 0,894 |
| Median (IQR) | 27,9(25-31) | 29,3(25-32) | |
| **BMR (kcal)**** | | | |
| Mean±SD | 1441,1 ±233,1 | 1516,6 ±284,1 | 0,894 |
| Median (IQR) | 1407(1308-1548) | 1448(1300-1660) | |
| **FFM (kg)**** | | | |
| Mean±SD | 47,9 ±7,2 | 50,1 ±9,7 | 0,089 |
| Median (IQR) | 46,4(43,4-50,9) | 47,1(42,9-53,7) | |
| **FM (kg)**** | | | |
| Mean±SD | 28,7 ±26,7 | 27,1 ±10,3 | 0,679 |
| Median (IQR) | 25,8(19,6-34,3) | 25,8(18,7-36,5) | |
| **Fat %**** | | | |
| Mean±SD | 34,8 ±8,4 | 34,3 ±8,2 | 0,739 |
| Median (IQR) | 35,7(29,7-41,1) | 34,8(29-40,3) | |
| **TBW (kg)**** | | | |
| Mean±SD | 34,9 ±5,8 | 36,7 ±7,1 | 0,075 |
| Median (IQR) | 34(31,7-37,3) | 34,5(31,4-39,3) | |
| **SBP (mm Hg)**** | | | |
| Mean±SD | 119,5 ±12,3 | 115,7 ±11,77 | 0,053 |
| Median (IQR) | 120(110-130) | 120(110-120) | |
| **DBP (mm Hg)**** | | | |
| Mean±SD | 72,5 ±9,6 | 71,2 ±9,4 | 0,405 |
| Median (IQR) | 70(63,7-80) | 70(60-80) | |
| **GHQ-12 **** | | | |
| Mean±SD | 12,2 ±6,7 | 10,7 ±5,9 | 0,178 |
| Median (IQR) | 10,5(7-16) | 9(6-14,5) | |

*Student T test, ** Mann-Whitney U test, ***Chi-square test

LT4: Levothyroxine, BMI: Body mass index, BMR: Basal metabolic rate, FFM: Fat-free mass, FM: Fat mass percentile, TBW: Total body water, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, GHQ-12: General Health Questionnaire-12. SD: Standard deviation.

**Table-2:** Thyroid hormone parameters of the groups.

| | Group 1 (n:110) | Group 2 (49) | P value |
|---|---|---|---|
| **TSH mU/L*** | | | |
| Mean±SD | 1,5 ±0,6 | 1,4 ±0,6 | 0,191 |
| Median (IQR) | 1,5(1,0-2,1) | 1,4(0,9-1,7) | |
| **FT4 ng/dl*** | | | |
| Mean±SD | 1,1 ±0,1 | 0,9 ±0,1 | 0,002 |
| Median (IQR) | 1,0 (0,9-1,1) | 0,9(0,8-1) | |
| **FT3 pg/ml*** | | | |
| Mean±SD | 2,7 ±0,4 | 2,9 ±0,3 | <0,001 |
| Median (IQR) | 2,6(2,3-2,9) | 2,8(2,7-3) | |

*Student T test, ** Mann-Whitney U test

TSH: Thyroid-stimulating hormone, FT4: Free throxine, FT3: Free triiodothyroinine, SD: Standard deviation.

**Table-3:** Laboratory parameters of the groups.

| | Group 1 (n:110) | Group 2 (49) | P value |
|---|---|---|---|
| **FPG (mg/dl)**** | | | |
| Mean±SD | 97,3 ±13,7 | 96,7 ±11 | 0,703 |
| Median (IQR) | 95(90-104) | 95(88,5-104,5) | |
| **HbA1c %**** | | | |
| Mean±SD | 5,8 ± ±0,7 | 5,8 ±0,5 | 0,687 |
| Median (IQR) | 5,8(5,5-6,1) | 5,8(5,6-6) | |
| **Creatinine(mg/dl)*** | | | |
| Mean±SD | 0,77 ±0,09 | 0,77 ±0,1 | 0,973 |
| Median (IQR) | 0,77(0,7-0,82) | 0,77(0,68-0,81) | |
| **CRP (mg/dl)**** | | | |
| Mean±SD | 0,34 ±0,3 | 0,27 ±0,2 | 0,198 |
| Median (IQR) | 0,2(0,2-0,38) | 0,2(0,2-0,2) | |
| **Ferritin (ng/ml)**** | | | |
| Mean±SD | 44,2 ±44,1 | 50,5 ±51,2 | 0,445 |
| Median (IQR) | 29,6(16,4-56,6) | 38,6(14,1-58,6) | |
| **Hb (g/l)**** | | | |
| Mean±SD | 13,2 ±1,3 | 13,1 ±1,4 | 0,794 |
| Median (IQR) | 13,2(12,5-14) | 13,1(12,4-14,3) | |
| **Hct (%)*** | | | |
| Mean±SD | 39,6 ±3,6 | 39,7 ±3,5 | 0,959 |
| Median (IQR) | 39,7(37,2-42) | 39,2(35,1-42,9) | |
| **TC (mg/dl)*** | | | |
| Mean±SD | 220,9 ±42,4 | 201,3±42,1 | 0,009* |
| Median (IQR) | 222,5(186,8-250,3) | 203(170,5-234,5) | |
| **LDL-C(mg/dl)*** | | | |
| Mean±SD | 139,8 ±39,5 | 127,8±33,7 | 0,071 |
| Median (IQR) | 142,8(110,1-165,7) | 124,4(109,9-157,2) | |
| **TG (mg/dl)**** | | | |
| Mean±SD | 137,4 ±77,6 | 111,2 ±48,2 | 0,032* |
| Median (IQR) | 118,5(77,7-170,7) | 110(66-148) | |
| **HDL-C (mg/dl)**** | | | |
| Mean±SD | 63,1 ±64,7 | 54,5 ±15,6 | 0,36 |
| Median (IQR) | 52(44-60) | 50(43-61,5) | |

*Student T test, ** Mann-Whitney U test

FPG: Fasting plasma glucose, HbA1c: Glycated haemoglobin, CRP: C-reactive protein, Hb: Haemoglobin, Hct: Haematocrit, TC: Total cholesterol, LDL-C: Low-density lipioprotien cholesterol, HDL cholesterol, TG: Triglycerides, HDL-C: High-density lipioprotien cholesterol.

## Discussion

The study evaluated the relationship between euthyroidism and metabolic parameters using lipid parameters and body composition analysis. In addition, it used GHQ-12 to assess psychological wellbeing.

LT4-treated patients had higher, but not significant, GHQ-12 level than the controls, which is similar to earlier findings.[13,14]

Djurovic et al. compared cognitive functioning and QOL in patients with Hashimoto's thyroiditis (HT) on long-term LT4 treatment and controls, and reported more anxiety and depression in the LT4-treated group, whicih may be associated with the significantly higher TSH levels reported in the LT4-treated group.[2]

In the current study, the non-significant increase in GHQ-12 scores in the LT4 group cannot be attributed to hypothyroidism alone. As Jonklaas mentioned, there are various conditions, such as chronic and psychiatric diseases as well as social and economic factors that contribute to psychological wellbeing and QOL. Apart from the euthyroid state, autoimmunity caused by Hashimoto may also result in morbidity. Also, thyroid function test is more likely to be overused, especially in patients with psychological distress and low mood. Besides, hypothyroidism as a chronic condition and awareness of the disease could also deteriorate patient's wellbeing.[15]

On the other hand, the American Thyroid Association (ATA) stated that despite normal serum TSH levels in LT4-treated patients, they may have low serum T3 levels.[1] As an expected finding, the current study revealed higher FT4 levels and lower FT3 levels in the LT4 group than the controls. Serum TSH radioimmunoassay, the reference marker of euthyroidism, is regulated by intracellular T3 in the pituitary gland. Therefore, de-iodinisation of the T4 to T3 is controlled by three different isoforms, and type 2 deiodinase (DOI2) is the main form in the pituitary to respond to circulating T4 levels. Researches have suggested conflicting results among different ethnicities about polymorphisms in the DOI2 gene which may be associated with low T3 levels and psychological wellbeing.[16]

In the current study, even though TSH levels were within the normal reference range in patients under LT4 treatment, serum TC and TG levels remained elevated. In a meta-analysis of 99 studies comparing 1,878 patients treated with LT4 and 14,493 healthy controls, TC and LDL-C remained elevated despite normalisation of TSH.[17] Lee et al. increased the LT4 dose to achieve reference range for TC and T3 levels, which resulted in suppression of TSH levels.[18]

Euthyroidism is related to energy metabolism that tissue hypothyroidism accompanying low FT3 levels may contribute to a BMR decrease.[19] Samuels et al. compared energy expenditure (EE) and body composition in patients under suppressive doses of LT4, chronic replacement dose, and euthyroid control subjects. Patients under replacement LT4 dose had lower resting EE (REE) than the suppressive-dose group and euthroid controls. FT3 was correlated with REE and was significantly lower in the LT4 replacement therapy group than the suppressive-dose group and the euthyroid controls, suggesting that LT4 treatment does not completely normalise EE.[20] In the current study, LT4-treated group had a lower but not significantly different BMR and FFM than the controls.

Further, patients under LT4 therapy and normal TSH levels with residual signs or symptoms may benefit from increasing LT4 dose to achieve the upper limit of T3, although this will result in lower TSH levels within the reference intervals. The other option may be the combination therapy using LT3 in selected cases. This treatment strategy appears to be advantageous for athyrotic patients, and a meta-analysis did not find any positive outcome.[21]

The current study has limitations. The GHQ-12 is a questionnaire to evaluate global QOL, and not a specific tool for particular conditions, like hypothyroidism. The possibility that these findings could be due to variations in patient characteristics cannot be ruled out. Also, since the study had a cross-sectional design, causality cannot be identified. Besides, the current study was a retrospective case-control study and did not calculate the power analysis.

Large-scale prospective studies are needed to evaluate the benefits of low-normal levels of TSH on psychological wellbeing and metabolic status.

## Conclusion

Thyroid hormone replacement needs to be adjusted to provide a satisfactory treatment for hypothyroid patients with normal TSH levels who remain clinically and biochemically asymptomatic. In symptomatic patients, peripheral parameters of hypothyroidism, such as lipid levels, physiological symptoms and QOL, might be useful in determining the levothyroxine dose and bringing the TSH level within the normal range.

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