RESEARCH ARTICLE

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Determinants of Levothyroxine Treatment in Patients with Hypothyroidism

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Abstract

BACKGROUND/AIMS: Hypothyroidism is a common disorder. Thyroid dysfunction and treatment failure can cause major health problems. Levothyroxine is the only treatment available for hypothyroidism. Its effectiveness depends on several factors. In this article, we aimed to determine which factors can cause hypothyroidism and how they affect its treatment.

MATERIALS AND METHODS: One hundred and eighty subjects with hypothyroidism who were referred to an endocrinology outpatient clinic were enrolled in this study. The patients were grouped according to treatment effectiveness. These groups were compared in terms of age, gender, medication adherence, thyroid autoantibodies [anti-thyroid peroxidase (anti-TPO) and anti-thyroglobulin (TG)], and thyroid heterogeneity. Co-ingested medications were investigated, and treatment effectiveness was compared.

RESULTS: The mean age was 46.8±12.8 years. One hundred and nine out of 162 patients were female (67.2%). Treatment failure was 55.6% (90/162). Patients with inadequate adherence to their levothyroxine treatment had higher anti-TPO and anti-TG levels (p=0.01). Ninety-three out of 162 patients (57.4%) had a medium/high adherence to levothyroxine therapy. Patients with low adherence (42.6%) experienced a higher treatment failure rate (p=0.01). Treatment failure rates did not vary according to gender or thyroid sonographic heterogeneity (p=0.49; p=0.66). Thirty-four out of 162 patients (21%) used medications which altered thyroid function. Additional medication use had an insignificant effect on thyroid-stimulating hormone levels (p=0.32).

CONCLUSION: These findings demonstrate high treatment failure rates, and that levothyroxine treatment adherence is an important subjective factor to determine treatment efficacy. Clinicians and patients should focus on underlying factors in order to increase treatment success.

Keywords: Hypothyroidism, levothyroxine, adherence, treatment efficiency, endocrinology

INTRODUCTION

Hypothyroidism affects a considerable fraction of the world population. Its prevalence varies according to country, gender, race, iodine status, region, and age group.[1] The prevalence of hypothyroidism is 24% in older adults (>65 years) in a United States population-based atherosclerosis risk in communities cohort.[2] According to a meta-analysis in Europe, thyroid dysfunction incidence in European countries is 5%.[3] The thyroid gland has important regulator, coordinator, and integrator roles in the body, and failure of treatment can result in serious health problems and, eventually, death.[4]

Levothyroxine is the only treatment choice for hypothyroidism. However, this treatment has several aspects to consider. Medication form (tablet, capsule, or liquid), patient adherence, and dosage times are the main considerations. Accompanying diseases and co-administered medications can interfere with levothyroxine absorption. The treatment of hypothyroidism depends on several factors. To avoid future health

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problems, such factors should be studied in order to have an effective treatment.

Therefore, in this study, we aimed to investigate levothyroxine treatment success rates in patients with hypothyroidism and to identify the influence of certain factors on treatment effectiveness.

MATERIALS AND METHODS

One hundred and eighty patients with hypothyroidism who were referred or admitted to the University of Health Sciences Turkey, İstanbul Training and Research Hospital Clinic of Endocrinology Outpatient between February, 2021 and January, 2022 were enrolled in this study. Their medical history was recorded, including age, gender, levothyroxine start time, dosage, operation history, accompanying diseases, and medication background. All laboratory examinations were carried out in the same laboratory. After overnight fasting before ingesting levothyroxine, a qualified laboratory staff-member took thyroid-stimulating hormone (TSH) and free T4 samples. TSH and free T4 were measured using the chemiluminescence method.

Additionally, other medications taken with levothyroxine and the place where levothyroxine was stored were investigated. The following patients were excluded: those who had chronic renal or hepatic failure; those diagnosed with malabsorption syndrome; malignancy; malignant thyroid disease; hypothyroidism after subacute hypothyroidism; central hypothyroidism; radioactive or drug-induced hypothyroidism; infiltrative disease associated with hypothyroidism; and pregnant patients. After exclusion, 162 patients were eligible for this study.

Levothyroxine adherence was measured using the validated Turkish version of the eight-item Morisky-Green test. This was performed by conducting face-to-face interviews. The patients were grouped according to their Morisky Medication Adherence Scores-8 [low adherence (<6); medium/high adherence (≥6)].[5-8]

Euthyroidism was defined as TSH levels between 0.4-4 mIU/mL. Patients with target TSH levels were compared with those patients with out-of-range TSH levels. The patients' age, gender, medication adherence, thyroid autoantibodies [anti-thyroid peroxidase (anti-TPO) and anti-thyroglobulin (TG)], and thyroid heterogeneity in ultra-sonographic examination were compared in terms of achieving their treatment goals.

Ethical approval was obtained from the University of Health Sciences Turkey, İstanbul Training and Research Hospital (approval number: 2021/2699). Written informed consent was obtained from all the patients. This study was conducted according to the Declaration of Helsinki principles.

Statistical Analysis

Statistical evaluations were performed using IBM SPSS 22.0 (Statistical Package for the Social Sciences software version 22.0). Descriptive results are expressed as median (minimum-maximum) or mean ± standard deviation and percentages (%). Shapiro-Wilk test was used for normality. The chi-square test or Fisher's exact test was used for categorical variables, where appropriate. Student's t-test was used for comparing the normality of distributed continuous variables of the two groups. The Mann-Whitney U test was used for comparing continuous variables that were not normally distributed between two groups.

Logarithmic transformation was used for continuous variables which were not normally distributed. Spearman correlations were used to investigate the relationships between different variables.

RESULTS

The mean age of the patients was 46.8±12.8 years. One hundred and nine out of the 162 patients were female (67.2%). Forty-nine out of the 169 patients (36%) used levothyroxine after undergoing a thyroid operation (Table 1). No difference was found in the treatment effectiveness between those patients who underwent thyroid operations and those who did not undergo thyroid operations (p=0.11). The treatment failure rate was 55.6% (90/162) for all patients. Those patients who experienced treatment failure had higher anti-TPO and anti-TG levels (p=0.01). Ninety-three out of the 162 patients (57.4%) had a medium/high adherence to levothyroxine therapy. Patients with low adherence to levothyroxine had a higher rate of treatment failure (p=0.01) Treatment failure did not vary in terms of gender or thyroid sonographic heterogeneity (p=0.49; p=0.66) (Table 2). According to our survey, 94.4% (153/162) of the patients used levothyroxine properly, half an hour before breakfast. 86.4% (140/156) of the patients kept their supply of levothyroxine at room temperature. Thirty-four out of the 162 patients (21%) used medications which altered thyroid function (Table 3). Those patients who used other medications had non significantly different TSH levels (p=0.32).

DISCUSSION

This study showed that the treatment failure rate in Turkish patients with hypothyroidism was relatively high (55.6%). According to the TSH levels in each patient, we demonstrated which factors determined the success of hypothyroidism management. We found that age, thyroid antibodies,

Table 1. General properties of the study group

Characteristic	Mean/frequency
Age (mean)	46.8±2.8
Male/female	53/109
Target level	52/162 (32.1%)
Treatment failure	90/162 (55.6%)
Over treatment (TSH <0.1 mIU/L)	7/162 (4.3%)
TSH: thyroid-stimulating hormone.	

Table 2. Differences between euthyroid patients and patients who experienced treatment failure

	Euthyroid	Treatment failure	p
Age (years) (n=155)	49.08±12.8	44.1±13.18	**0.04**
Male/female	22/44	30/59	0.79
TSH (mIU/L) (n=155)	2.71±1.50	7.90±3.44	**<0.01**
Free T4 (ng/L) (n=135)	4.24±4.44	3.77±4.07	0.63
Anti-TPO (IU/mL) (n=128)	154.9±220.6	497.73±630.2	**0.01**
Anti-TG (IU/mL) (n=120)	159.9±335.8	692.13±197.6	**0.01**
Thyroid ecogenity	32/42	67/90	0.66
Adherence (medium/high)	37/49 (64.1%)	48/87 (55.1%)	**0.03**

Significant values were expressed in bold, anti-TPO, and anti-TG.
TSH: thyroid-stimulating hormone, anti-TPO: anti-thyroid peroxidase, anti-TG: anti-thyroglobulin.

and treatment adherence were the factors which determined the success of hypothyroidism treatment. Our study included a broad evaluation, in which all factors involved in levothyroxine treatment were evaluated.

A study in Colorado examining 25,862 patients found that 40% of patients taking thyroid replacement therapy had out-of-range TSH levels.[9] Another study in India found that 41.7% of patients were undertreated.[10] It is important to understand what the reasons for the high treatment failure rate is. Our study tried to answer this question by evaluating several factors. The available treatment choice for hypothyroidism is levothyroxine tablets, and they are available only in capsule form in many countries. Levothyroxine is absorbed 20-30 minute after tablet intake and it takes nearly three hours to finalize its absorption stage.[8] Therefore, any factor which disrupts this process should be considered. We concluded that treatment adherence is one of the most important factors. We observed that, in those patients who failed in achieving their treatment goals, their treatment adherence was significantly lower (55.1%), whereas, in the sufficiently treated group, treatment adherence was 64.1% (p=0.03). In all study groups, treatment adherence was 57.4%. In a study examining 289 patients, 72.2% had a medium/high adherence to levothyroxine.[11] In another study, this ratio was 85.8%. However, these studies did not compare their adherence ratios with therapeutic effectiveness.

Despite low-medium adherence, we found that a high proportion of patients correctly obeyed the levothyroxine intake time. A majority of patients took levothyroxine at least half an hour before breakfast (94.4%). Several studies and reviews support the practice of delaying mealtimes for at least 30-60 minute after tablet ingestion.[12-14] A recent meta-analysis showed that levothyroxine intake half an hour before dinner was equally effective.[15] Another study which examined the effect of proton pump inhibitors (PPIs) co-administration in patients with hypothyroidism showed that serum TSH levels increased with PPIs.[16] Another study showed that calcium carbonate increased TSH levels in those patients using levothyroxine.[13] We found that a significant number of patients used medications which altered levothyroxine absorption or function (21.0%), but this did not affect TSH levels. According to another study, other medications did not affect TSH levels.[17]

Thyroid antibodies (anti-TG and anti-TPO) were significantly higher in the treatment failure group. Likewise, a study from Korea demonstrated that increased TPO antibody was found as a helper prognostic factor in subclinical hypothyroidism (SCH). In this study, high anti-TPO levels were associated with less improvement in thyroid function.[18] Although increased anti-thyroid antibody levels may indicate the likelihood of overt hypothyroidism, no correspondence of antibody level and risk for overt hypothyroidism has been found in most of the studies.[19] A

study of 204 SCH patients showed sustained TSH elevation in patients receiving levothyroxine who had initially diffuse thyroiditis pattern in ultrasonography. Along with the anti-thyroid antibody positivity, the decline in thyroid functions increased.[20] The fact that anti-TPO antibodies not only elevate oxidative stress and glycosylation products, but also damage thyrocytes and block enzyme activity could explain these findings.[21] Therefore, high anti-thyroid antibodies could cause inflammation to become more severe and these patients may require higher doses of levothyroxine.

Study Limitations

The limitations of this study include the following: 1) dietary habits and ingredients were not evaluated; 2) this was a single-center and cross-sectional study. However, it included a significant number of patients and evaluated multiple factors in hypothyroidism treatment.

CONCLUSION

These findings demonstrate high treatment failure, and that adherence to levothyroxine treatment is an important subjective factor in determining treatment efficacy. Thyroid autoantibody levels and age were significant factors as well. Clinicians and patients should focus on underlying factors in order to increase treatment success.

MAIN POINTS

- Treatment success in patients with hypothyroidisim depends on several factors.

- 180 patients with hypothyroidism have been included in the study.

- Co-administered medications didn't seem to affect treatment success in hypothyroid patients

- Levothyroxine adherence was lower and thyroid auto antibodies were higher in the in patients who have not achieved treatment levels.

ETHICS

Ethics Committee Approval: This study was approved by the Ethics Committee for Clinical Research of the University of Health Sciences Turkey, İstanbul Training and Research Hospital (approval number: 2021/2699).

Informed Consent: Written Informed consent was obtained from all the patients.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: S.K., Concept: S.K., Y.H., Design: S.K., Y.H., Data Collection and/or Processing: S.K., Y.H., Analysis and/or Interpretation: S.K., Literature Search: S.K., Writing: S.K.

DISCLOSURES

Conflict of Interest: No conflict of interest was declared by the authors.

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Table 3. Additional factors in treatment	
Subjective factors	**Frequency**
Levothyroxine time (at least half an hour before breakfast)	153/162 (94.4%)
Levothyroxine storage place (room temperature, far from sunlight)	140/156 (86.4%)
Use of medications altering levothyroxine absorption	34/162 (21.0%)
Use of medications which do not alter levothyroxine absorption	39/162 (24.1%)

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