

## **Misuse of levothyroxine and the rate of achieving target thyroid-stimulating hormone in levothyroxine treatment.**

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### **Abstract**

**Objectives:** The aim of the present study was to investigate the misuse of levothyroxine treatment in patients with hypothyroidism.

**Methods:** Patients who received levothyroxine treatment were included in the study. Age, gender, duration of medication use, Thyrotropin (TSH) level, regular use of medication, time and manner of taking medication, drug storage conditions and use of additional medication were recorded. Taking the medication on a full stomach or in the evening, occasional use of medication, storing the medicine in the refrigerator, and the use of additional medication were classified as misuse of levothyroxine treatment. According to the levels of TSH: 0.4-4.5 mIU/L was considered a normal dose, while 4.5 mIU/L and above was considered insufficient, and 0.4 mIU/L and below was considered as high dose.

**Results:** Patients who received levothyroxine pill were included in the study (average age: 53 ± 14 years, average duration of medication use: 48 ± 50 months and females/male ratio: 363/44). 323 (79.4%) of patients stated that they take the medicine regularly. Levothyroxine dosage was found to be sufficient in 235 patients (57.7%), insufficient in 101 patients (24.8%) and high in 71 patients (17.4%). Among the 84 patients which were identified as misusing, 66 (16.2%) patients were taking the medicine on a full stomach, 12 (2.9%) patients were taking the medicine in the evening, 11 patients (2.7%) were storing the medicine in the refrigerator, 17 (4.2%) patients were taking the medicine occasionally, and 21 (5.1%) patients were using one or more additional medications.

**Conclusions:** Taking the medication on a full stomach or in the evening, occasional use of medication, storing the medicine in the refrigerator, and the use of additional medications were the major factors for insufficient TSH levels. Appropriate usage of levothyroxine pills is crucial for successful treatment.

**Keywords:** Levothyroxine treatment, Rate of achieving target thyroid-stimulating hormone, Misuse of levothyroxine.

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### **Introduction**

Levothyroxine is used in the treatment of low or insufficient thyroid hormones [1]. Levothyroxine should be taken as a single dose with water on an empty stomach at least 30 min before eating in the morning, and should not be taken with another medication [2,3]. As levothyroxine preparations may not have the same therapeutic efficacy at the same doses, treatment should be maintained with identical preparations. Thyroid hormone absorption can be affected by age, celiac

disease, malabsorption, and Proton Pump Inhibitors (PPI), as levothyroxine preparations are dissolved in an acidic environment [4]. Drug interactions with iron preparations, antacids such as aluminium hydroxide, cholestyramine, sucralfate, and calcium may affect the absorption of levothyroxine [5-7]. These types of drugs should be taken at least 4 hours after levothyroxine administration.

Some sources state that levothyroxine tablets can be taken in the evening [8,9]. However, levothyroxine is most often

administered in the morning, on an empty stomach, in order to increase its oral absorption [2,3,9-11].

Up to 80% of levothyroxine taken orally is absorbed by the upper part of the small intestine. Effects begin 3-5 days after oral intake. The average half-life of levothyroxine is 7 days. Levothyroxine preparations should be protected from light and stored at room temperature (below 25°C) [12].

According to the levels of TSH: 0.4-4.5 mIU/L was considered a normal dose, while 4.5 mIU/L and above was considered insufficient, and 0.4 mIU/L and below was considered as high dose [9,13].

Taking the medication on a full stomach or in the evening, only occasional use, storage in the refrigerator and the use of additional medication are common types of misuse of the levothyroxine treatment. There are few studies in the literature on the misuse of levothyroxine [14,15].

Many studies have shown that taking levothyroxine on an empty or full stomach. Gastric acidity and drug interactions affect plasma levels of levothyroxine, but the proportion of the patients is affected by this condition in clinical practice has not been investigated until now. Moreover, during evaluation of thyroid function tests which are not in a normal range, mistakes associated with levothyroxine use are usually not considered by physicians [15]. In our study, we aimed to investigate the common mistakes of patients using levothyroxine treatment.

**Subjects and Methods**

A total of 407 patients who received levothyroxine pills were included in the study. Institutional Ethics permission was obtained from the Rize Findikli Goiter Research and Treatment State Hospital in Turkey in 25-November-2014 (approval number: 2417/2014). Age, gender, duration of medication use, TSH level, indications for use, regular use of medication, time and manner of taking medication (on a full/empty stomach, morning and evening, occasionally), drug storage conditions (storing in refrigerator), use of supplementary medications (iron, Proton Pump Inhibitor (PPI), antacid, etc.), and drug dosage information were recorded. Taking the medication on a full stomach or in the evening, occasional use of medication, storing the medicine in the refrigerator, and the use of additional medication were classified as misuse. In the treatment of levothyroxine, TSH levels of 0.4-4.5 mIU/L were considered a normal, 4.5 mIU/L and above as insufficient and 0.4 mIU/L and below as a high dose.

Patients aged 15 years and above receiving levothyroxine treatment due to hypothyroidism or operated goitre and

patients receiving levothyroxine treatment for at least 6 months were included in the study. Patients undergoing levothyroxine treatment for less than 6 months, patients with thyroid cancer or central hypothyroidism, and patients with gastrointestinal disease were excluded from the study.

**Statistical analysis**

Statistical analysis was performed using the SPSS 18.0 software program. Categorical variables were expressed in numbers or percentages, and the continuous variables were expressed by mean ± standard deviation. Categorical variables were compared using the Chi-square test. For continuous variables, the Kolmogorov-Smirnov test was used first to test the normal distribution of the parameters. The independent samples t-test was used to compare data for normal distribution. A probability value of p<0.05 was considered statistically significant.

**Results**

A total of 407 patients receiving levothyroxine were included in this study (average age: 53 ± 14 years; average duration of medication use: 48 ± 50 months; female/male ratio: 363/44). 323 (79.4%) patients stated that they take the medicine regularly. Levothyroxine dosage was found to be sufficient in 235 patients (57.7%), insufficient in 101 patients (24.8%) and high in 71 patients (17.4%). Among the 84 patients identified as misusing, 66 (16.2%) patients were taking the medicine on a full stomach, 12 (2.9%) patients were taking the medicine in the evening, 11 patients (2.7%) were storing the medicine in the refrigerator, 17 (4.2%) patients were taking the medicine only occasionally, and 21 (5.1%) patients were using one or more additional medications.

Fifty-one (77.3%) patients who received levothyroxine treatment on a full stomach had higher level of TSH, while 11 (16.7%) had normal levels and 4 (6.1%) had lower levels of TSH. The level of TSH was found to be insufficient in 16 (94.1%) patients skipping levothyroxine pills occasionally, whereas TSH levels were higher in 11 (100%) patients storing levothyroxine preparation in the refrigerator, and TSH levels were found to be higher in 15 (71.4%) patients taking additional medication. The majority of the patients were female. No statistically significant differences were found between males and females in terms of rate of achieving target TSH level, average age, duration of drug use, indications for use, rate of regular use and misuse rates.

Results are summarized in Tables 1 and 2.

*Table 1. Characteristics of patients according to TSH levels.*

Parameter	All patients	TSH: below 0.4		TSH: between 0.4-4.5		TSH: above 4.5	
		High dosage	levothyroxine	Sufficient levothyroxine dosage	Insufficient levothyroxine dosage		

n (%)	407	71 (17.4)	235 (57.7)	101 (24.8)
Mean age (years)	53 ± 14	55 ± 12	53 ± 14	51 ± 14
Female/Male	363/44 (89.2/10.8)	60/11	215/20	88/13
Duration of use (months)	48 ± 50	49 ± 44	48 ± 53	47 ± 48
<b>Indications</b>				
Post thyroidectomy	227 (55.8)	50 (22)	134 (59)	43 (19)
Primary hypothyroidism	180 (44.2)	21 (11.7)	101 (56.1)	58 (32.2)
Regular use of levothyroxine	323 (79.4)	67 (20.7)	221 (68.4)	35 (10.8)
<b>Misuse of levothyroxine pills</b>				
Taking on a full stomach	66 (16.2)	4 (6.1)	11 (16.7)	51 (77.3)
Taking in the evenings	12 (2.9)	1 (8.3)	1 (8.3)	10 (83.3)
Storing in the refrigerator	11 (2.7)	0 (0)	0 (0)	11 (100)
Taking the medicine occasionally	17 (4.2)	0 (0)	1 (5.9)	16 (94.1)
Use of additional medication	21 (5.1)	3 (14.3)	3 (14.3)	15 (71.4)
*Proton pump inhibitor	14 (3.4)	3 (21.4)	2 (14.2)	9 (64.3)
*Antacid	13 (3.2)	2 (15.4)	1 (7.7)	10 (76.9)
*Iron	7 (1.7)	0 (0)	0 (0)	7 (100)
Dosage administered	96 ± 33	114 ± 36	90 ± 30	96 ± 34

**Table 2.** Analysis of the patients according to gender.

Parameter	Female	Male	P-value
n (%)	363 (89.2)	44 (10.8)	
The rate of achieving target TSH	214 (59)	20 (45.5)	0.087
Mean age (years)	52 ± 14	54 ± 14	0.538
Duration of use (months)	49 ± 52	41 ± 33	0.35
<b>Indications</b>			
Post thyroidectomy	201 (55.4)	26 (59.1)	0.639
Primary hypothyroidism	162 (44.6)	18 (40.9)	0.639
Regular use	288 (79.3)	35 (79.5)	0.974
<b>Misuses</b>			
Taking on a full stomach	59 (16.3)	7 (15.9)	0.953
Taking in the evenings	11 (3)	1 (2.3)	0.779
Storing in the refrigerator	10 (2.8)	1 (2.3)	0.852
Taking the medicine occasionally	17 (4.7)	0 (0)	0.143
Use of additional medication	19	2	0.912
Dosage administered	95 ± 31	100 ± 50	0.345

## Discussion

In the literature, few studies have examined the misuse of levothyroxine treatment and rates of achieving target TSH

levels. Similarly, few studies have been conducted on gender-based differences in levothyroxine misuse. Thus we aimed to investigate the characteristics of the levothyroxine misuse in terms of the rate of the achieving target TSH levels and gender-based differences.

In a multi-centered study conducted on the patients with hypothyroidism receiving levothyroxine treatment in India, abnormal TSH levels were found in 1051 (54.6%) patients and the levels of TSH was above 4.0 mIU/L in 808 (41.97%) patients, and below 0.4 mIU/L in 243 (12.62%) patients [14]. No data regarding levothyroxine misuse was provided in that study. In a study conducted on patients with hypothyroidism receiving levothyroxine treatment, the TSH levels were found to be normal range in 74% of the patients; TSH levels were high in 17.5% of patients and low in 8.5% of patients [15]. In that study, taking medication on a full stomach, storing in the refrigerator, and taking additional medication were considered major misuse of medication [15].

In a study conducted on patients with hypothyroidism secondary to thyroidectomy, TSH levels were normal in 59% of the patients, TSH levels were suppressed in 23% of the patients and TSH levels high in 18% of the patients [16]. Similarly, in our study, TSH levels were found to be normal in 59% of the patients taking levothyroxine for those with hypothyroidism secondary to thyroidectomy.

Taking levothyroxine pill on a full stomach will require higher doses of levothyroxine compared to taking it on an empty stomach to achieve the target level of TSH [17]. In the present

study, TSH was found to be high in 77.3% of the patients who took levothyroxine on a full stomach.

Levothyroxine dosage usually is 1.6 µg/kg body weight, which is 100 to 150 µg/kg for men and 75 to 100 µg/kg for women [18]. The aim of the treatment is to normalize the serum TSH levels [19]. Thyroid hormones can also directly modulate circulation and peripheral vascular beds. So that levothyroxine sufficient dosage was very important [20]. The higher TSH levels demonstrate insufficient dosage of the levothyroxine treatment, the lower TSH levels demonstrate over-dosage of the levothyroxine treatment and normal TSH levels show sufficient dosage of the levothyroxine treatment. In the present study levothyroxine dosage was found sufficient in 235 (57.7%) patients, insufficient in 101 (24.8%) patients, and high in 71 (17.4%) patients.

One or more misuse of levothyroxine pills was detected in 84 patients in the present study. For the most common misuse of levothyroxine pills, 66 (16.2%) patients were taking the pills on a full stomach, 12 (2.9%) patients were taking the pills in the evening, 11 patients (2.7%) stored the pills in the refrigerator, 17 (4.2%) patients were taking the pills occasionally, and 20 (4.9%) patients were using one or more additional pills.

We also investigated gender in terms of achieving the target TSH level. The ratio of the achieving the target TSH level was found 45.5% in males and 59.0% in females. No statistically significant differences were found between genders in terms of the investigated parameters.

## Conclusion

In the present study, we demonstrated that the rate of the achieving target level of TSH was 57.7%. Medication misuse was found in 20.6% of the patients. Major factors for insufficient values of TSH levels include taking medication on a full stomach or in the evening, occasional use of medication, storing the medicine in the refrigerator, and the use of additional medication. Patients should be made aware of proper storage and use of levothyroxine pills, as these are crucial for successful treatment.

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## Conflict of Interest

There is no conflict of interest

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