

COMPLIANCY TO LEVOTHYROXINE TREATMENT AND THE RATE OF DISEASE CONTROL FOR PATIENTS WITH HYPOTHYROIDISM IN DUHOK CITY

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ABSTRACT

Background: Hypothyroidism is one of the most prevalent endocrine diseases, affecting nearly 200 million people globally, with around 60% of those affected remaining undiagnosed. The incidence of hypothyroidism has been shown to have increased recently, becoming a worldwide health problem. It accounts for 30-40% of the patients seen in endocrinology departments and clinics. Iodine deficiency is the most prevalent cause of hypothyroidism, with data showing that around 2 billion people suffer from insufficient iodine intake.^{ke}

Materials and Methods: In this cross-sectional study, we enrolled 309 adults with hypothyroidism who had been receiving Levothyroxine for 8 weeks or more at Azadi General & Teaching Hospital from July 10, 2023, to August 25, 2023. The planned sample size was chosen to facilitate accurate estimates of the rate of control and adherence to treatment. No formal study visits were conducted, and patients were approached for participation during their routine clinic visits.

Results: In our study of 309 hypothyroidism patients treated with levothyroxine for 8 weeks to 25 years, we found that 54.37% achieved optimal disease control, 37.22% did not achieve control, and 8.41% were overcorrected. Patients with full adherence to levothyroxine had significantly better TSH control compared to those with poor adherence ($p < 0.001$).

Conclusions: In this study, we observed poor treatment compliance rates, with only around half of the patients achieving disease control. Additionally, a significant proportion of patients were found to be overweight or obese.

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Keywords: Hypothyroidism, Levothyroxine, subclinical hypothyroidism and Hashimoto's disease.

Hypothyroidism stands as a pervasive endocrine disorder, affecting nearly 200 million individuals worldwide, yet a staggering 60% of cases remain undiagnosed⁽¹⁾, despite its widespread prevalence, a concerning trend emerges with approximately 60% of individuals affected by hypothyroidism remaining undiagnosed, and this substantial proportion of undetected cases underscores the challenges in early detection and diagnosis, potentially leading to untreated conditions and subsequent health complications⁽²⁾. Recent evidence indicates a noteworthy increase in the incidence of

hypothyroidism, marking it as a significant health concern globally⁽³⁾.

In clinical settings, hypothyroidism accounts for a substantial portion, estimated at 30-40%, of patients seeking care in endocrinology departments and clinics, this trend underscores the growing burden of hypothyroidism on healthcare systems and emphasizes the importance of proactive measures to address its prevalence and impact effectively, as the number of diagnosed cases continues to rise, strategies focusing on early detection, accurate diagnosis, and comprehensive management become increasingly essential

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to mitigate the consequences of this widespread endocrine disorder^(3,4). In the developed world, the incidences of both hypothyroidism and subclinical hypothyroidism are reported to be 4.5% and 4-15%, respectively⁽³⁻⁶⁾. Data obtained from the National Health and Nutrition Examination Survey (NHANES) indicates an increase in the prevalence of HT from 9.5% in 2012 to 11.7% in 2019. Additionally, more than 78% of patients were administered thyroxin (T4) monotherapy⁽⁷⁾.

Iodine deficiency stands as the most prevalent cause of hypothyroidism, with approximately 2 billion individuals worldwide suffering from insufficient intake of iodine, this essential mineral plays a crucial role in the synthesis of thyroid hormones, and inadequate iodine levels can lead to thyroid dysfunction and hypothyroidism, on the other hand, autoimmune thyroid disease remains the most common cause of hypothyroidism in developed countries and regions with sufficient iodine intake. Autoimmune thyroid diseases, such as Hashimoto's thyroiditis, occur when the body's immune system mistakenly attacks the thyroid gland, leading to inflammation and impaired thyroid function. Despite adequate iodine intake, autoimmune thyroid disease can still develop, highlighting the complex interplay of genetic, environmental, and immunological factors in thyroid health^(8,9).

The disease disproportionately affects women, with a ratio of 10 women to every 1 man impacted by hypothyroidism, while the exact reasons for this imbalance are not fully understood, hormonal differences and genetic predispositions are believed to play key roles in contributing to the higher prevalence of hypothyroidism among women⁽¹⁰⁾. The disease arises from insufficient production of thyroid hormones by the thyroid gland, resulting in

an inability to meet the body's metabolic demands, this deficiency leads to a decrease in the metabolic rate within target tissues throughout the body, as thyroid hormones play a crucial role in regulating metabolism, energy production, and various physiological processes, their inadequate production can disrupt the body's normal functioning⁽¹¹⁾. The metabolic slowdown caused by insufficient thyroid hormone levels can contribute to weight gain and alterations in lipid profiles, increasing the risk of cardiovascular disease. Hypothyroidism-related hypertension, particularly diastolic hypertension, can further elevate cardiovascular risk and strain on the heart. Cognitive disorders, including memory impairment and difficulty concentrating, may result from reduced thyroid hormone activity affecting brain function. Infertility can arise due to disruptions in the menstrual cycle and ovulation in women, while men may experience decreased libido and sperm production. Neuromuscular symptoms such as muscle weakness, cramps, and stiffness may also occur, impacting mobility and physical function⁽¹²⁻¹⁴⁾.

Numerous recent studies have consistently demonstrated that hypothyroidism is associated with a lower quality of life when compared to the general population. The impact of hypothyroidism on quality of life can be multifaceted, encompassing physical, emotional, and social dimension⁽¹⁵⁾. Levothyroxine (LT4) is a highly effective and widely used drug for treating hypothyroidism worldwide. Its primary objective is to resolve symptoms and signs of hypothyroidism and restore normal metabolic and biochemical activity, aiming to achieve a Thyroid Stimulating Hormone (TSH) concentration within target ranges (0.4-3IU/ml). However, despite treatment and follow-up, some studies indicate that a significant proportion of hypothyroid patients (40-

49%) are either under- or over-treated⁽¹⁵⁻²⁰⁾. Moreover a suboptimal compliance to LT4 treatment is seen in a large percentage of patients because it's either forgotten by the patients or because they have to delay their breakfast by 30 minutes or more⁽²¹⁾.

The objective of this study was to assess the rate of disease control and estimate the compliance to Levothyroxine (LT4) treatment among patients diagnosed with hypothyroidism and subclinical hypothyroidism. Additionally, the study aimed to investigate whether the timing of LT4 dosing influenced the rate of disease control. By examining these factors, the study aimed to provide insights into the effectiveness of LT4 treatment in managing thyroid disorders and identify potential factors influencing treatment outcomes.

MATERIALS AND METHODS:

In this cross-sectional study, we enrolled 309 adults diagnosed with hypothyroidism and subclinical hypothyroidism, all of whom were receiving Levothyroxine treatment for 8 weeks or longer at Azadi General & Teaching Hospital between July 10, 2023, and August 25, 2023. The planned sample size was carefully chosen to enable precise estimates of the rate of control and adherence to treatment within the study population. No formal study visits were conducted; instead, patients were invited to participate during their routine clinic visits. Upon obtaining consent, all patients underwent detailed interviews to gather information on disease diagnosis, treatment dosage, and adherence. Subsequently, blood samples were collected to measure thyroid hormone levels for further analysis.

Statistical analyses:

The general and medical characteristics of patients with hypothyroid were presented in mean (SD) or no (%). The prevalence of TSH among hypothyroid patients was determined in number and percentage. The prevalence of TSH among patients with

different characteristics was examined in a Pearson chi-squared test. The predictors of uncontrolled compared to the controlled TSH among hypothyroid patients were determined in a nominal logistic regression. The significant level of difference was identified in a $p < 0.05$. The statistical calculations were performed using the JMP Pro 14.3.0 (https://www.jmp.com/en_us/home.html).

RESULTS:

In this study, we included 309 patients diagnosed with hypothyroidism and treated with levothyroxine for durations ranging from 8 weeks to 25 years. The age range of the patients varied from 16 to 85 years, with a mean age of 43.92 years. The majority of patients fell between the ages of 30 to 50 years. Obesity emerged as the most prevalent health issue, with only 36 (11.65%) patients classified as having a normal weight and body mass index (BMI) below 25, while the remaining 273 (88.35%) patients were overweight or obese, with BMIs ranging from 18.62 to 51.42 and a mean BMI of 31.11. Hypertension was also commonly detected among the study participants, with 124 (40.13%) patients affected. Regarding medication administration, 227 (73.46%) patients took the medicine in the morning before breakfast, while 82 (26.54%) patients ingested it at bedtime or just before the morning praying time. Among those, 173 (55.99%) patients took the drug daily without missing any doses, while the remainder missed one dose or more per month. Out of the participants, 169 (54%) reported a positive family history of hypothyroidism, while 34 (11%) of them had a previous history of hyperthyroidism, data illustrated in table 1.

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Table 1: General and medical characteristics of patients with hypothyroid patients

Characteristics (n=309)	Statistics	
	Number	Percentage
Age (16-85 years) mean (SD)	43.92	11.54
Age category		
20-29	20	6.47
30-39	99	32.04
40-49	94	30.42
50-59	60	19.42
60-69	27	8.74
70-79	7	2.27
80-89	2	0.65
Sex		
Male	43	13.92
Female	266	86.08
Disease duration		
0-3 years	182	58.90
4-6 years	61	19.74
7-10 years	40	12.95
> 10 years	26	8.41
Family history		
Negative	140	45.31
Positive	169	54.69
FT4 (1.79-160) mean (SD)	14.24	2.207
Thyroxine (25-200) mean (SD)	84.04	30.55
BMI (18.61-51.42) mean (SD)	31.11	5.25
BMI category		
Normal weight	36	11.65
Overweight	97	31.39
Obesity class I	102	33.01
Obesity class II	51	16.51
Obesity class III-IV	23	7.44
Hypertension		
No	185	59.87
Yes	124	40.13
Time of ingestion		
Morning	227	73.46
Night	82	26.54
Missed medicine doses/month (1-15)		
Not missed	173	55.99
1-3 doses	118	38.19
4-5 doses	14	4.53
>5 doses	4	1.29
Previous Hyperthyroidism		
No	275	89.00
Yes	34	11.00

In this study, we found that around 168 (54.37%) patients had optimal control of the disease, with their TSH levels within the reference range for their age. Additionally, 115 (37.22%) patients were

not controlled, as their TSH levels were above the references, and 26 (8.41%) patients were overcorrected, with TSH below target values. Please refer to Table 2 and Figure 1 for detailed data presentation.

Table 2: Prevalence of TSH among hypothyroid patients

TSH (n=309)	Count	Percentage
Controlled	168	54.37
Uncontrolled	115	37.22
Over correction	26	8.41

TSH Category

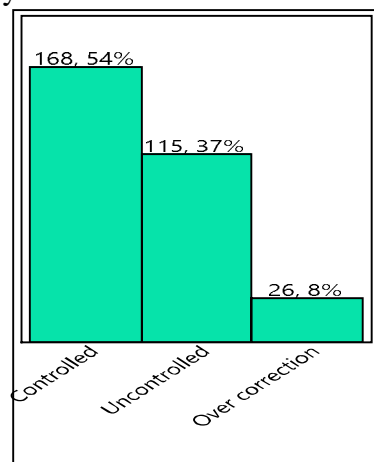


Fig 1: Prevalence of TSH control among hypothyroid patients

As depicted in Table 3, patients aged below 30 years and those aged older than 60 years exhibit significantly lower TSH control compared to those aged 30 to 60 years, who demonstrate better TSH control (p-value < 0.001). We found no significant

differences in TSH control between males and females (p-value = 0.4099). Additionally, the duration of the disease does not impact the control rate (p-value = 0.223). Patients with hypertension exhibit better disease control than non-hypertensive patients (p-value = 0.0191), but there are no significant differences between patients with different BMI (p-value = 0.1069). The rate of TSH control increases as compliance improves; patients with more missed doses have more uncontrolled disease, with a highly significant p-value of < 0.001. Furthermore, patients taking Thyroxin doses of 75mcg and more exhibits significantly better disease control compared to those taking 50mcg or less (p-value < 0.001).

Table 3: Prevalence of TSH among hypothyroid patients with different general and medical characteristics

Characteristics (n=309)	TSH Category			P (two-sided)
	Controlled (168, 54.37%)	Over correction (26, 8.41%)	Uncontrolled (115, 37.22%)	
Age category				
20-29	5 (25.00)	0 (0.00)	15 (75.00)	
30-39	64 (64.65)	4 (4.04)	31 (31.31)	
40-49	55 (58.51)	6 (6.38)	33 (35.11)	
50-59	32 (53.33)	4 (6.67)	24 (40.00)	<0.0001
60-69	11 (40.74)	7 (25.93)	9 (33.33)	
70-79	1 (14.29)	4 (57.14)	2 (28.57)	
80-89	0 (0.00)	1 (50.00)	1 (50.00)	
Sex				
Male	27 (62.79)	2 (4.65)	14 (32.56)	0.4099
Female	141 (53.01)	24 (9.02)	101 (37.97)	
Disease duration				
0-3 years	92 (50.55)	12 (6.59)	78 (42.86)	
4-6 years	38 (62.30)	6 (9.84)	17 (27.87)	0.2223
7-10 years	22 (55.00)	6 (15.00)	12 (30.00)	
> 10 years	16 (61.54)	2 (7.69)	8 (30.77)	
Family history				
Negative	82 (58.57)	11 (7.86)	47 (33.57)	0.3985
Positive	86 (50.89)	15 (8.88)	68 (40.24)	
BMI category				
Normal weight	17 (47.22)	2 (5.56)	17 (47.22)	0.1069
Overweight	64 (65.98)	6 (6.19)	27 (27.84)	
Obesity class I	55 (53.92)	9 (8.82)	38 (37.25)	
Obesity class II	24 (47.06)	7 (13.73)	20 (39.22)	
Obesity class III-IV	8 (34.78)	2 (8.70)	13 (56.52)	

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Characteristics (n=309)	TSH Category			P (two-sided)
	Controlled (168, 54.37%)	Over correction (26, 8.41%)	Uncontrolled (115, 37.22%)	
Hypertension				
No	102 (55.14)	9 (4.86)	74 (40.00)	0.0191
Yes	66 (53.23)	17 (13.71)	41 (33.06)	
Time of ingestion				
Morning	121 (53.30)	22 (9.69)	84 (37.00)	0.3970
Night	47 (57.32)	4 (4.88)	31 (37.80)	
Missed medicine doses/month				
Not missed	129 (74.57)	19 (10.98)	25 (14.45)	<0.0001
1-3 doses	38 (32.20)	6 (5.08)	74 (62.71)	
4-5 doses	1 (7.14)	1 (7.14)	12 (85.71)	
>5 doses	0 (0.00)	0 (0.00)	4 (100.00)	
Previous Hyperthyroidism				
No	151 (54.91)	26 (9.45)	98 (35.64)	0.0810
Yes	17 (50.00)	0 (0.00)	17 (50.00)	
Thyroxine				
25	4 (33.33)	1 (8.33)	7 (58.33)	<0.0001
50	33 (40.24)	4 (4.88)	45 (54.88)	
75	31 (58.49)	3 (5.66)	19 (35.85)	
100	81 (66.94)	8 (6.61)	32 (26.45)	
125	10 (47.62)	3 (14.29)	8 (38.10)	
150	7 (38.89)	7 (38.89)	4 (22.22)	
200	2 (100)	0 (0.00)	0 (0.00)	

Pearson chi-squared test was performed for statistical analyses.

In this study, we observed that patients with full compliance to levothyroxine therapy (no missed doses) exhibit a better TSH control rate compared to those with poor adherence, with a highly significant p-value of < 0.001. Additionally, when comparing patients aged 20-29 with older age groups (30-39, 40-49, 50-59), we found a better control rate as the age increased, with significant p-values of 0.0061, 0.0069, and 0.0149, respectively. Patients receiving LT4 doses of 75mcg and larger also demonstrated a better control

rate compared to those receiving 50mcg or less (p-value = 0.01836). Participants with increased BMI showed no significant differences in the control rate when compared with those with normal BMI when LT4 dosing was included. However, when LT4 dosing was not included, there was a significant control rate for higher BMI compared to lower BMI, with significant p-values. Please refer to Table 4 for detailed data analysis.

Table 4: Predictors of uncontrolled compared to the controlled TSH among hypothyroid patients a: with doses of medicines b: without including doses of medicine

A: predictors (n=283)	Outcome: Uncontrolled TSH (with including medicine doses)		
	OR (95% CI)	Presentations	P
Missed medicine doses/month			0.00000
1-3 doses/ Not missed	10.61 (5.51 to 20.42)		<0.0001
4-5 doses/ Not missed	79.23 (8.78 to 715.41)		<0.0001
Thyroxine	0.17 (0.04 to 0.76)		0.01836
Age category			0.14303
20-29/30-39	6.53 (1.71 to 24.97)		0.0061
20-29/40-49	7.26 (1.72 to 30.56)		0.0069
20-29/50-59	7.02 (1.46 to 33.72)		0.0149
Hypertension			0.22301
No/ Yes	1.64 (0.74 to 3.64)		0.2269

A: predictors (n=283)	Outcome: Uncontrolled TSH (with including medicine doses)		
	OR (95% CI)	Presentations	P
BMI category			0.22531
Obesity class I/ Normal weight	2.13 (0.66 to 6.91)		0.2089
Obesity class II/ Normal weight	2.89 (0.72 to 11.52)		0.1333
Obesity class III-IV/ Normal weight	4.98 (0.88 to 28.26)		0.0697
Time of ingestion			0.32364
Morning/ Night	1.49 (0.67 to 3.34)		0.3266
Disease duration			0.37503
7-10 years/4-6 years	2.45 (0.70 to 8.59)		0.1609
0-3 years/4-6 years	2.09 (0.85 to 5.18)		0.1097
Sex			0.54054
Female/ Male	1.35 (0.52 to 3.52)		0.5423
Previous Hyperthyroidism			0.76031
Yes/ No	1.16 (0.46 to 2.93)		0.7601
Family history			0.78668
Positive/ Negative	1.09 (0.57 to 2.09)		0.7866
B: predictors (n=283)	Outcome: Uncontrolled TSH (without including medicine doses)		
	OR (95% CI)	Presentations	P
BMI category			0.02394
Obesity class III-IV/ Normal weight	4.84 (1.24 to 18.95)		0.0234
Obesity class III-IV/ Obesity class I	3.74 (1.23 to 11.41)		0.0202
Obesity class II/ Overweight	2.72 (1.17 to 6.37)		0.0208
Obesity class III-IV/ Overweight	5.92 (1.85 to 18.93)		0.0027
Age category			0.03475
20-29/30-39	6.51 (1.92 to 22.08)		0.0026
20-29/40-49	4.68 (1.28 to 17.08)		0.0194
Hypertension			0.05626
No/ Yes	1.88 (0.97 to 3.64)		0.0603
Family history			0.22416
Positive/ Negative	1.39 (0.82 to 2.35)		0.2251
Previous Hyperthyroidism			0.35915
Yes/ No	1.44 (0.66 to 3.12)		0.3583
Time of ingestion			0.38801
Morning/ Night	1.35 (0.68 to 2.65)		0.3907
Disease duration			0.46177
0-3 years/> 10 years	1.41 (0.54 to 3.72)		0.4848
7-10 years/4-6 years	1.33 (0.48 to 3.64)		0.5827
> 10 years/4-6 years	1.23 (0.41 to 3.69)		0.7180
0-3 years/4-6 years	1.73 (0.84 to 3.56)		0.1352
0-3 years/7-10 years	1.30 (0.56 to 3.05)		0.5402
Sex			0.83173
Female/ Male	1.09 (0.49 to 2.41)		0.8321

Nominal Logistic was performed for statistical analysis.

DISCUSSIONS:

In this study of patients suffering from Hypothyroidism in Duhok city, we aimed to estimate the rate of compliance to treatment and the prevalence of control among them. The overall prevalence of high compliance (no missed doses in 1 month) in this study was 55.99%, which is higher than that observed in a cross-sectional study of 337 patients conducted in Lebanon, where the prevalence was

45.1%(22) Furthermore, the prevalence of high compliance (no missed doses in 1 month) in our study among patients suffering from Hypothyroidism in Duhok city was notably higher than that found in a study from Oman, where the compliance rate was reported at 26%(23) Additionally, in a cross-sectional study of 420 patients from Saudi Arabia, the high compliance rate was reported at 10%, further highlighting the comparatively higher

compliance observed in our study among patients suffering from Hypothyroidism in Duhok city. (24) However, when compared to studies conducted in developed countries, our study showed a lower compliance rate. For instance, an observational cross-sectional study among 320 adult patients with hypothyroidism in Italy reported an 87% high compliance rate, indicating a significantly higher adherence to treatment compared to our findings (25).

In this study, we observed that around 168 (54.37%) patients achieved optimal control of the disease, with their TSH levels within the references for their age. Additionally, 115 (37.22%) patients were not controlled, as their TSH levels were above the references, and 26 (8.41%) patients were overcorrected, with TSH below target values. These findings were lower than those observed in a cross-sectional study conducted in Colorado State, where 33,661 subjects presented to the 118 Colorado Health Fair screening sites. Among the 1525 (5.9%) individuals who reported taking thyroid medication at the time of the survey, 60% of them had TSH within the target ranges, and 20% had suppressed TSH levels (26). However our findings were nearly similar to a study conducted in the UK, which included 18,944 patients on levothyroxine treatment. The study revealed that 53% of them had TSH levels within the target range, while 27% had TSH levels above the normal range, and 20% had TSH levels below the normal range. (27).

In this study, we found a non-significantly higher disease control rate of 57% in night dosing compared to 53.3% in morning dosing, similar results were found in a randomized trial of 82 patients conducted in Basra (28). In contrast, Bolk et al., in a pilot study involving 12 women with primary hypothyroidism, revealed that LT4 taken at bedtime significantly improved the levels of thyroid hormone

(29). The same researchers in 2017 conducted a randomized crossover double-blind trial involving 105 patients, they confirmed once again the previous finding of improvement of thyroid hormone levels in patients treated with night-time dosing (30).

The prevalence of overweight and obesity in our study was estimated to be 88.35% (273 patients), these results were higher compared to the 75.6% found in hypothyroid patients in a study conducted in Spain (31).

CONCLUSIONS:

In this study, we observed a poor rate of compliance to treatment, with around half of the patients experiencing uncontrolled disease. Additionally, most of the patients were found to be overweight or obese.

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پوخته

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پیشہ کی و نارمانج:

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الخلاصة

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..... الخلفية والأهداف:

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