



## Timing of Levothyroxine in the Treatment of Primary Hypothyroidism

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### Authors' contributions

This work was carried out in collaboration between all authors. Authors JHA and AAM designed the study, wrote the protocol, performed the statistical analysis and wrote the first draft of the manuscript. Author ZNANAE recruited the patients, collected the data and carried out literature search. All authors read and approved the final manuscript.

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### ABSTRACT

**Aim:** Timing of levothyroxine (L-thyroxine) administration seems beneficial for early obtaining thyroid state. The present study aimed at investigating the best time of L-thyroxine administration that can achieve earlier normalization of thyroid stimulating hormone (TSH) and free thyroxine (FT4) levels in patients with primary hypothyroidism.

**Study Design:** Eighty two patients with primary hypothyroidism were recruited between November 2012 and July 2013 during their consultation to Al-Faiha Specialized Diabetes, Endocrine and Metabolism Center, Basrah, Iraq. The patients were divided into two equal groups; group A were receiving L-thyroxine daily, one hour before breakfast, group B: the dose of L-thyroxine was given at the evening. TSH, FT4, Body mass index (BMI), blood pressure, lipid profile were measured before, 30, 60 and 90 days after treatment with L-thyroxine.

**Results:** The mean reduction in TSH from baseline for the evening treatment was  $13.6 \pm 22.2$  mIU/ml which was slightly and insignificantly higher than the value of the morning treatment

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(11.3±22.5 mIU/ml),  $P = .63$ ,  $df = 80$ , 95% CI: -12.17, 7.5). The mean increase in FT4 from baseline for the evening treatment was 5.7±4.9 pmol/l which was lower than 7.6±6 pmol/l in the morning treatment, ( $P = .12$ ,  $df = 80$ , 95% CI: - 0.5, 4.3). There was no effect of treatment timing on lipid profile, blood pressure, and BMI.

**Conclusions:** There were no differences between the morning and evening treatment with L-thyroxine on early normalization of TSH and FT4.

**Keywords:** L-thyroxine; primary hypothyroidism; TSH; FT4.

## ABBREVIATIONS

**TSH:** Thyroid Stimulating Hormone; **FT4:** Free Thyroxine; **BMI:** Body Mass Index; **FT3:** Triiodothyronine; **TPO:** Thyroid Peroxidase; **SPSS:** Statistical Package for Social Sciences.

## 1. INTRODUCTION

Hypothyroidism is one of the most common endocrine disorders with a prevalence rate in the general population ranging from 3.8%–4.6% [1], while the prevalence of overt hypothyroidism varies according to different surveys between 0.1 and 2% [2].

Many *in vivo* biological parameters including thyroid hormones are reported to follow circadian rhythm, with a variation in their levels during the day [3]. One study has reported that TSH, FT3 and FT4 levels follow diurnal rhythm reaching a peak level at mid night and a trough level at 2 pm in patients with hypothyroidism on thyroxine replacement therapy [4]. Understanding these phenomena may help achieve optimum pharmacological effects, minimizing side effects, and improving quality of life [5] and additionally, stimulating interest in conducting studies aiming at achieving early normalization of TSH and FT4 with alternating dose administration of L-thyroxine between morning and evening. Not too many studies were performed in this area, nonetheless the obtained results are controversial. Bolk et al. in 2007 and 2010 [6,7] studied the effect of the best time of dosing on thyroid hormones and found that the evening dosing is superior to the morning dosing in obtaining euothyroid state. conversely, Rajput and coworkers [8] found no differences between morning and evening dosing.

This study was designed to investigate the best time of administering L-thyroxine that can achieve earlier normalization of TSH and FT4 in patients with primary hypothyroidism.

## 2. PATIENTS AND METHODS

One hundred and eight patients with primary hypothyroidism were enrolled in the study during

their consultation to Al-Faiha Specialized Diabetes, Endocrine and Metabolism Center (FDEMC). The study was an open-label, therapeutic, outpatient-based and included both males and females in the age range: 20 – 85 years with primary hypothyroidism (if the patient was new, TSH should be equal or more than 10 mIU/l). The diagnosis of primary hypothyroidism and criteria for patients selection were made according to a work published elsewhere [2].

### 2.1 Exclusion Criteria

The patients were excluded if they have thyroid cancer, transient hypothyroidism and thyroiditis, subclinical hypothyroidism, patients receiving sequestrants of bile acid, antacids containing aluminum hydroxide, sodium polystyrene sulfonate, raloxifene, phenobarbital, phenytoin, carbamazepine, rifampicin. Patients with secondary hypothyroidism, diabetes and pulmonary, cardiac, renal, and gastrointestinal diseases were excluded as well. Pregnant women, those delivered within 3 months and lactating women were also excluded. Twenty six patients were excluded, one woman became pregnant, two patients did not comply with treatment, 23 patients (21%) did not return back after the first visit.

### 2.2 Study Setting

Eighty two patients had completed the study; 41 patients were treated with L-thyroxine in the morning (group A) and 41 patients in the evening (group B). The two groups were matched for sex, age, BMI, duration and severity of the disease (TSH and FT4 levels) and were randomly selected for treatment assignment. Initial sample size was estimated by recruiting patients to achieve 80% power of a test to detect 10% difference in TSH and FT4, using a formula for one-tailed unpaired t-test [9]. The sample size

was recalculated after exclusion of patients. Assignment of treatment to each group depends on patient's drug history; if they were using L-thyroxine at night before enrollment in the study, the timing of the dose was shifted to the morning and vice versa. For newly diagnosed patients who were not yet started treatment, were then randomly divided and allocated to either treatment timing. The study protocol was approved by the College Council and the Ethical Committee of the College of Medicine, University of Basrah, and written informed consents were obtained from patients.

The study was carried out from November 2012 to July 2013. A baseline value of FT4, TSH, and lipid profile were taken and repeated after three months. FT4 was measured monthly during the three-month study period. BMI and blood pressure were taken at baseline and after 3 months.

The first group was assigned to receive L-thyroxine dose (L-thyroxine 100 Berlin-Chemie, Menarini international, Florence, Italy) with a glass of water in the morning, one hour before breakfast, while the second group received the dose in the evening two hours after the last meal. The effect of food on absorption of L-thyroxine tablets was discussed with patients and were encouraged to comply with one type or a range of light foods as much as possible.

A starting dose of 100 mcg/day was given if TSH level was more than 60 mIU/l, or a dose of 50 mcg was given when the level less than 60 mIU/l. The dose was then gradually escalated according to FT4 level. If the thyroid state (normalization of FT4 and TSH) was not achieved, the dose of L-thyroxine was increased by 25 mcg/day to a maximum dose of 150 mcg/day.

### 2.3 Laboratory Investigations

Serum TSH and FT4 were measured by enzyme immunoassay (enzyme-linked fluorescent assay) by minividas using VIDAS TSH or FT4 kits, France). Serum was stored at  $-25\pm 6^{\circ}\text{C}$  for up to 2 months until analysis. The normal range of TSH is between 0.5 and 5 mIU/l and for FT4 (9-20 pmol/l).

Fasting s. glucose, total cholesterol and its fractions HDL-C, LDL-C, VLDL-C and triglyceride were measured by enzymatic colorimetric assay by Analyticon Biolyzer using Fluitest kit, Germany.

Thyroid peroxidase (TPO) antibodies were measured by immunometric enzyme immunoassay by ELISA Biotek 800, USA using demeditec kit, Germany. Normal value was considered if the titer is less than 50 IU/l, those with a titer of 50-75 IU/l was considered negative and elevated if the titer is more than 75 IU/l.

### 2.4 Statistical Analysis

SPSS version 15 was used for statistical analysis. Independent sample t-test was used for mean comparison of the two groups; paired t-test was used for comparing mean changes within the group between baseline and three months values. The data are expressed as mean  $\pm$  SD, *P*-value < .05 is considered significant.

### 3. RESULTS

Eighty two patients had completed the study, their characteristics are listed in Table 1. The baseline value of TSH of the morning treatment (group A) was  $17.9\pm 20$  mIU/ml which was significantly reduced to  $6.5\pm 9.2$  mIU/ml after three months treatment with L-thyroxine, *P*-value < .001, with a mean difference of reduction from baseline of  $11.3\pm 22.5$ .

For the evening treatment (group B), TSH was significantly declined from a baseline value of  $19.7\pm 22$  to  $7.7\pm 10.4$  after three months treatment with L-thyroxine, *P*-value < .001, with a mean difference of reduction from baseline of  $13.6\pm 22.2$ . The mean difference of reduction in TSH from baseline for the two treatments was compared and found slightly higher for the evening treatment, but it did not achieve statistical significance, *P* = .63, *df* = 80, 95% CI: -12.17, 7.5 (Table 2, Fig. 1).

The reduction in TSH was associated with an increase in FT4. The baseline value of FT4 for the morning treatment was  $7.9\pm 3$  pmol/l which was significantly increased to  $15.7\pm 5.1$  pmol/l after three months treatment with L-thyroxine, *P*-value < .001, with a mean difference of increase from baseline of  $7.6\pm 6$  pmol/l. For the evening treatment, FT4 was significantly increased from a baseline value of  $9.94\pm 3.7$  to  $15.7\pm 3.7$  pmol/l after three months treatment with L-thyroxine, *P*-value < .001, with a mean difference of increase from baseline of  $5.7\pm 4.9$  pmol/l. Comparing the difference of increase in FT4 for the two treatments ( $7.6\pm 6$  vs  $5.7\pm 4.9$ ) pmol/l, no significant differences were detected, *P* = .12, *df* = 80, 95% CI: - 0.5, 4.3 (Table 2, Fig. 1).

### 3.1 Secondary Parameters

Serum lipid profile, fasting s.glucose, BMI and blood pressure were almost the same for the two treatments and statistical differences were not obtained, apart from a small reduction in the BMI for the evening treatment (group B) in comparison with the morning treatment (group A).

## 4. DISCUSSION

The study was principally aimed at investigating the best time during the day, for the administration of L-thyroxine to patients with primary hypothyroidism in order to achieve earlier normalization of TSH and FT4.

TSH, the most sensitive parameter was reduced in the two groups treated with L-thyroxine but the reduction in the evening group was slightly and insignificantly higher than the morning group. This reduction in TSH is paralleled with elevation in FT4 levels. These observations are in agreement with Rajput and co-workers [8] who found no significant difference in thyroid profile between the morning and evening treatment with L-thyroxine. In contrast, Bolk et al. [6], in a pilot study on 12 women with primary hypothyroidism, revealed that L-thyroxine taken at bedtime significantly improved the levels of thyroid hormone but such changes failed to improve parameters of quality of life and lipid profiles. In 2010, the same researchers, in a randomized

crossover double-blind trial including 105 patients, have further confirmed previous observation of improvement of thyroid hormone levels in patients treated with night-time dosing [7]. Although the mechanism behind variation in response to morning or evening L-thyroxine treatments and associated variation in thyroid hormones are not well understood, however, many possibilities are put forward; first, absorption of L-thyroxine takes place mainly in the jejunum and ileum within three to four hours of ingestion [10]. Absorption of L-thyroxine needs adequate gastric acidity to dissolve the salt-based tablet allowing for intestinal absorption [11]. As a result, variation in basal acid secretion between morning and evening, at which acid secretion is maximum in the evening and lowest in the morning [12], may favor absorption of L-thyroxine in the evening and that may contribute in reducing TSH level.

Food can interfere with absorption of L-thyroxine and may emerge as a factor involved in variation of response [13,14], however, for the present study the researchers were fully aware of this matter and all possible precautions and advices were taken into consideration to account for this effect. After oral dose of thyroxine, 60%–80% is absorbed irrespective to thyroid state and the absorption decreases in the presence of food from 79% under fasted conditions to 64 % after food for a 100 mcg dose [15]. Type of food and eating habit could also have an impact on L-thyroxine absorption.

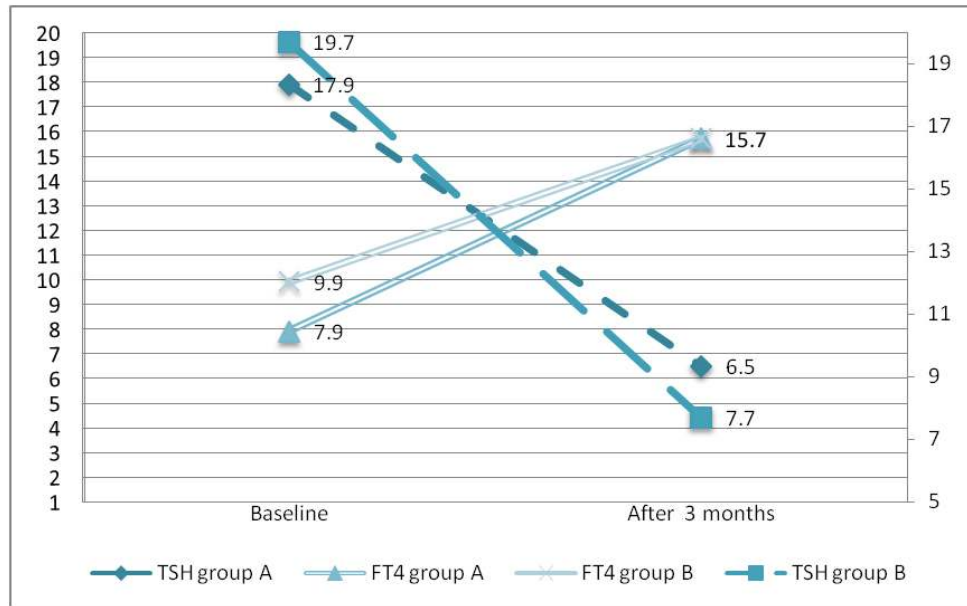
**Table 1. Patients' characteristics**

<b>Characteristics</b>	<b>Morning group N = 41</b>	<b>Evening group N = 41</b>
Age-year (mean $\pm$ SD)	47 $\pm$ 11	48 $\pm$ 13
Male to female ratio	4:37	9:32
BMI median (range)	31.6 (22-44)	30.8 (21-48)
Number of patients on other drugs	28	24
<b>Etiology of hypothyroidism</b>		
Hashimotos disease	28	29
Others: Idiopathic, Hashimotos thyroiditis + surgery	7	5
Thyroidectomy	5	7
Radioactive iodine	1	0
<b>Dose of L-thyroxine (<math>\mu</math>g)</b>		
Median (range)	100 (50-150)	100 (50-150)
Mean $\pm$ SD	93 $\pm$ 29	104 $\pm$ 23
TSH (mIU/l) (mean $\pm$ SD)	17.9 $\pm$ 20	19.7 $\pm$ 22
FT4 (Pmol/l) (mean $\pm$ SD)	7.9 $\pm$ 3	9.9 $\pm$ 3.7
Duration of hypothyroidism (months) (mean $\pm$ SD)	44 $\pm$ 55	56 $\pm$ 79

**Table 2. Morning and evening TSH and FT4 levels following treatment with L-thyroxine (Mean ± SD)**

Variable	Morning group (group A, n = 41)			Evening group (group B, n = 41)		
	Baseline	3 months	Difference	Baseline	3 months	Difference
TSH (mIU/ml)	17.9±20	6.5±9.2*	11.3±22.5	19.7±22	7.7±10.4*	13.6±22.2
FT4 (pmol/l)	7.9±3	15.7±5.1*	7.6±6	9.94±3.7	15.7±3.7*	5.7±4.9
BMI	31.4±4.7	31.8±5	0.39±3.5	31.5±5	30.6±5	0.9±1.3

\* Significantly different from the corresponding baseline level; P < .001



**Fig. 1. Relationship between changes in TSH at baseline and after 3 months with changes in FT4 after treatment with L-thyroxine for the morning and evening treatment**

Second, another possible explanation for changes in thyroid hormones in response to L-thyroxine treatment may result from the fact that the metabolism of L- thyroxine takes place in target tissues, in part by deiodination to T3 [16]. The activity of this enzyme has been found reduced at night, resulting in reduction of thyroxine metabolism with elevated thyroxine level [17], however, in view of the complex relationships between the enzyme activity and thyroid hormones, the net result of reduction in activity of the deiodinase enzyme, elevation of T4, reduction of T3 and their effect on TSH level is not well understood. Two factors; time of blood sampling and maintaining on the same brand of L- thyroxine which were thought to influence the study outcome were carefully considered. Blood samples in the present study were collected in the morning irrespective of dosing with L-thyroxine whether given in the morning or evening. It may be argued that morning blood sampling is suitable for monitoring thyroid hormones with morning dosing but not with

evening dosing, however, it has been shown in some studies that morning blood sampling is suitable for monitoring thyroid hormones whether L-thyroxine treatment is given in the morning or evening [8].

Regarding the L- thyroxine tablets, the same brand of L- thyroxine was used to avoid differences in potency and to ensure bioequivalence and thus makes interchangeability between the tablets possible. Generally, it is recommended to encourage the use of a consistent thyroxine preparation for individual patients to minimize variability from refill to refill [18].

### 5. CONCLUSION

It can be concluded that there were no differences between the morning and evening treatment with L-thyroxine with regards to earlier normalization of TSH and FT4.

## COMPETING INTERESTS

Authors have declared that no competing interests exist.

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