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Original Article

Early Morning Vs Bed Time Administration of Levo-thyroxine – A Comparative Study

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ABSTRACT

Background: *Levothyroxine is a commonly prescribed drug in the treatment of patients with hypothyroidism. Levothyroxine is traditionally administered in the morning, on an empty stomach, to increase its absorption. However, many patients have trouble for taking levothyroxine in the morning.* ***Aim and objectives:*** *The aim of this study was to evaluate the effect of changing administration time of levothyroxine from before breakfast to bed time on serum levels of TSH & serum FT4.* ***Methods:*** *This was a prospective, longitudinal, comparative study. 60 Participants who were stable on morning dosage of levothyroxine were instructed to take LT4 tablets at bed time and another 60 participants who were stable on bed time dosage were instructed to take the drug at morning at least 1 hour before breakfast. After 3 months Serum TSH and serum FT4 was measured.* ***Results:*** *In the present study, changing the administration time of levothyroxine before breakfast to bed time, resulted in decreased in the serum levels of TSH also decreased level of serum FT4 levels but were insignificant and negligible (P > 0.05). And changing the administration time of levothyroxine from bed time to before breakfast, resulted in increased in the serum levels of TSH, and also increased in serum FT4 levels but were insignificant and negligible (P value > 0.05.)* ***Conclusions:*** *So levothyroxine can be given either before breakfast or at bed time without any significant change in serum TSH and FT4.*

Key words: Levothyroxine, TSH, FT4.

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INTRODUCTION

Hypothyroidism is the result of inadequate production of thyroid hormone and the inadequate action of thyroid hormone in target tissues. Primary hypothyroidism is the main cause of hypothyroidism. Hypothyroidism is a common endocrine disorder and is more prevalent in elderly women and in certain ethnic groups. In a Study in Bangladesh have reported the prevalence of hypothyroidism to be 7%.[1] Hypothyroidism may be either clinical/overt, with elevation in the TSH and low levels of FT4, or subclinical, with normal levels of FT4 and elevated level of TSH. Hypothyroidism can arise as primary from the thyroid gland when there is a defect in thyroid hormone synthesis and release centrally from the hypothalamic-pituitary-thyroid axis when there is a defect in either TRH or TSH signaling to the thyroid.

Hypothyroidism is permanent in most patients and requires lifelong thyroid hormone replacement. Typically, levothyroxine (L-thyroxine) is the primary treatment for hypothyroidism, which has a low cost and few side effects [2, 3]. It is used for replacement therapy due to its consistent potency and prolonged duration of action. On oral administration, absorption of thyroxine occurs in the stomach and small intestine and is incomplete. About 80% is absorbed, and it is slightly increased when taken in empty stomach [4]. Interference with absorption has been seen with sucralfate, iron sulfate, calcium preparations, aluminum antacids, activated charcoal, food items, and herbal remedies [5-7]. Fiber-enriched diet also shows reduced bioavailability of levothyroxine [8, 9].

Optimally, L-thyroxine should be taken on an empty stomach at least 60 minutes before a meal. There is a great debate regarding the best timing for administration of L-thyroxine. There have been contradictory results with regard to the best timing to take L-thyroxine. Some studies supported L-thyroxine intake at bedtime [10, 11]. While other studies supported L-thyroxine intake during early morning fasting [12]. Yet, some other studies found no timing difference in this regard [13]. Up to our knowledge there is no such studies in Bangladeshi population. So this study was done to see the effect of morning vs bed time administration of levo-thyroxine on Serum TSH and FT4.

METHODS

This prospective, longitudinal, comparative study conducted in a private chamber of medicine specialists in Khulna city. Study period was August 2020- July2021. Total number of participants is 120.

Inclusion criteria: 1) Age ≥ 18 years; 2) Primary hypothyroidism; 3) Using levothyroxine for at least 6 months and have been on stable doses for the last 3 months.

The study procedures will be explained to those who meet the inclusion criteria, and those who provide written informed consent will be enrolled. Until the target population is achieved.

Exclusion criteria: 1) Severe organic syndrome, dementia, thyroid cancer, heart failure (functional class IV); 2) Three or more hospital admissions in the last year; 3) Refusal to participate; 4) Who take drug irregularly

The participants were divided into 2 groups: Group A & Group B. 60 participants were included in each group.

Before changing time of levothyroxine administration Serum TSH and FT4 was measured and recorded. The serum concentration values of 0.39-6.1 µIU/mL for TSH and 0.6- 1.8 ng/dL for FT4 was considered normal.

Group A: 60 Participants who were stable on morning dosage of levothyroxine were instructed to take LT4 tablets at bed time.

Group B: 60 participants who were stable on bed time dosage were instructed to take the drug at morning at least 1 hour before breakfast.

After 3 months Serum TSH and serum FT4 was measured.

RESULTS

In our study female & male ratio was 5:1. Mean age of our patients was 37±13.2 years. Most of the patients (54.1%) were is age group of 30-40 years. 45.8 % patients BMI was > 30. 97% patents don't have any family history of hypothyroidism. Hyperlipidemia was the most common (32%) comorbidity.

Table 1: Demographic characteristics of the patients (n=120).

Age groups	
18-30 years	**20 (16.6 %)**
30-40 years	**65 (54.1 %)**
>40 years	**35 (29.1 %)**
Body mass index (BMI)	
19-25	**25 (20.8 %)**
25-30	**40 (33.3 %)**
>30	**55 (45.8 %)**
Familial history of hypothyroidism	
Yes	**23 (19.16 %)**
No	**97 (80.8 %)**
Concurrent disease	
None	**41 (34.16 %)**
Hyperlipidemia	**32 (26.6 %)**
Hypertension	**28 (23.33 %)**
Iron deficiency anemia	**19 (15.8 %)**

In group A:

Mean (SD) S TSH before changing from morning to bedtime was 2.96 (1.3) mIU/dl, after 3 months mean S TSH was 2.88 (1.08) mIU/dl resulting p value of > 0.05 (insignificant).

Mean S FT4 (SD) before changing from morning to bedtime was 1.33 (.38) ng/dl, after 3 months mean was S FT4 1.32 (0.24) ng/dl resulting p value of > 0.05 (insignificant).

Table 2: Mean (SD) Serum TSH & Mean Serum FT4 changes in Group A

Parameters	**Baseline**	**At 3 months**	**p Value**	**Remarks**
S TSH	2.96	2.88	.35	Insignificant
S FT4	1.33	1.32	.43	Insignificant

In group B:

Mean S TSH before changing from bedtime to morning was 3.82 (1.04) mIU/dl; after 3 months mean S TSH was 3.85 (.85) mIU/dl resulting p value of > 0.05 (insignificant).

Mean S FT4 before changing from bedtime to morning was 1.25 (.36) ng/dl after 3 months mean S FT4 was 1.27 (.32) ng/dl resulting p value of > 0.05 (insignificant).

Table 3: Mean (SD) Serum TSH & Serum FT4 changes in Group B

Parameters	Baseline	At 3 months	p value	Remarks
S TSH	3.82	3.85	.44	Insignificant
SFT4	1.25	1.27	.37	Insignifican

DISCUSSION

The current therapeutic procedure for hypothyroidism is mainly focused on hormone replacement therapy by sodium levothyroxine. The patients are usually advised to take the medication in the morning 30-60 minutes before breakfast. However, for many patients, this time schedule is not appropriate and they feel more comfortable to take the medication in the evening. In this study, the effect of changing levothyroxine administration time from morning to evening, according to serum levels of TSH and T4 was evaluated. The effects of changing the levothyroxine administration time on serum TSH and T4 levels was previously studied [10, 12-14].

In the present study, changing the administration time of levothyroxine before breakfast to bed time, resulted in decreased in the serum levels of TSH, but not statistically significant (P=.35). There is also changes in serum FT4 levels but were insignificant and negligible (P=.43) In our study, changing the administration time of levothyroxine from bed time to before breakfast, resulted in increased in the serum levels of TSH, but not statistically significant (P=.44). There is also increased in serum FT4 levels but were insignificant and negligible (P= .37).

In a randomised cross over study[12] sixty five adult study subjects were chosen and randomised into three 8 week regimens (fasting, bedtime, with breakfast) in a three period crossover design. Mean serum TSH levels was significantly high in bedtime group (2.19 mIU/L) when compared to before breakfast group (1.06 mIU/L) ($p<0.001$). In another study there is a 1.25 µIU/ml increase in the average serum level of TSH as a result of changing the levothyroxine administration time form morning to evening [12]. Result of our study is contradictory with these studies.

Our study corresponds to a retrospective review done in 2001 and found the decrease in mean serum TSH level (0.286±1.722mIU/L) when levothyroxine supplementation was changed from morning to midnight but did not show any statistical significance ($p=0.532$)[13]. Similar results were found in several other studies [14-16]. Some other studies found equal efficacy of the two administration times [17, 18]. The results of few studies showed a significant improvement in the thyroid hormone profile of patients after switching from morning to the evening dose [19, 20].

LIMITATIONS

1) Interval between food intake and levothyroxine intake was not considered in this study**; 2)** Interaction with other drugs in regards of absorption of Levothyroxine was not considered.

CONCLUSION

The dosage of levothyroxine which maintained euthyroid status (as reflected by TSH and FT4 level) when taken in early morning empty stomach is also likely to maintain euthyroid status when it is administered at bedtime. So Patients may be allowed to choose either morning or bedtime regimen depending on their convenience.

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