



Levothyroxine Administration Timing in Hypothyroidism Patients

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Authors' contributions

This work was carried out in collaboration among all authors. Author MSDAI designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors SMRA, RHMA, KASA, NSEA and TAA managed the analyses of the study. Authors MFHA, LSSA, AAB, AAZS, DMSF and AAYA managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Levothyroxine is a synthetic T4 hormone that is biochemically and physiologically identical to the natural hormone, and it is used when the body is deficient in the natural hormone. This study was conducted to summarize the current evidence that compare evidence supporting morning dose to evening dose of levothyroxine in patients with hypothyroidism .A simple systematic review was carried out, searching databases PubMed, Google Scholar, and EBSCO. The authors extracted the needed data. There is conflicting data regarding effectiveness of morning dose versus evening

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dose in management of levothyroxine. More studies reported effectiveness of bedtime dose more than breakfast dose in hypothyroidism management. Numerous studies reported effectiveness of bedtime dose more than breakfast dose in hypothyroidism management. The most recent evidences recommended that, if possible, L-T4 be consistently taken either 60 minutes before breakfast or at bedtime (3 or more hours after the evening meal), for optimal, consistent absorption.

Keywords: levothyroxine; hypothyroidism; dose timing.

1. INTRODUCTION

Thyroid hormones play an important role in the human body and, as such, their deficiency necessitates therapy [1]. Hypothyroidism may have serious consequences for one's wellbeing and quality of life (QOL), as it is linked to weakness, weight gain, cold aversion, depression, neuromuscular symptoms, diastolic dysfunction, and renal function deficiency. It is also linked to cardiovascular risk such as hyperlipidemia, hyperhomocystinemia, and arterial hypertension, especially when thyroid hormone supplementation is inadequate [2].

Levothyroxine is a synthetic T4 hormone that is biochemically and physiologically identical to the natural hormone, and it is used when the body is deficient in the natural hormone [3]. The treatment of major, intermediate, and tertiary hypothyroidism with oral levothyroxine is the main indication. It is also used to treat euthyroid goitres, such as thyroid nodules, subacute or chronic lymphocytic thyroiditis, multinodular goitre, or thyroid cancer patients who have undergone thyroidectomy, as well as as an alternative to surgery and radioiodine treatment [4].

Levothyroxine is mostly absorbed in the small intestine, especially the duodenum, jejunum, and ileum. In the intestine, just a small amount is consumed. As a result, patients with shorter small intestines (bowel resection) have lower absorption and need higher levothyroxine doses. The absorption of levothyroxine tends to be affected by gastric pH [5].

While levothyroxine has long been used to treat hypothyroidism, the proper usage is sometimes unclear. Thyroid hormone levels are not only regulated by responsive and complicated feedback processes, but they are also influenced by illness, food consumption, and the use of concomitant medicine [6]. While these conflicting aspects can be difficult for physicians to understand, a clear understanding of these

components, as well as other PK concerns, would potentially benefit the patient [7].

To improve absorption, levothyroxine is often given on an empty stomach in the morning. When taking the hormone alongside magnesium, iron, some meats, and other medications, the absorption of levothyroxine in the gut is reduced. As a result, patients are generally advised to take levothyroxine on an empty stomach 30-60 minutes before food consumption to prevent erratic hormone absorption. Many patients, however, have difficulty taking levothyroxine in the morning [8]. As a result, several trials have been conducted to assess the effectiveness of the evening dosage of levothyroxine.

However, there is conflicting data regarding effectiveness of morning dose versus evening dose in management of levothyroxine. More studies reported effectiveness of bedtime dose more than breakfast dose in hypothyroidism management.

This study was conducted to summarize the current evidence that compare evidence supporting morning dose to evening dose of levothyroxine in patients with hypothyroidism.

2. METHODOLOGY

A simple systematic review was carried out, searching databases PubMed, Google Scholar, and EBSCO using the following terms in different combinations: levothyroxine, absorption, morning dose, evening dose and hypothyroidism along with other key words. We included all full texts [randomized controlled trials, observational, review articles and experimental studies in making up of this study]. The authors extracted qualitative data, and then the author's names, year, study type, methodology, and the result were reported (Table 1). Inclusion criteria included all relevant studies with similar objectives as our study. Time and language restrictions were made to 20 years and English language due to lack of translation sources.

Exclusion criteria included all studies irrelevant to our topic and papers published 20 years ago or more. No software has been utilized to analyze the data. The data was extracted based on specific form that contains (Author's name, publication year, country, methodology and

results). These data were reviewed by the group members to determine the initial findings, and the modalities of performing the surgical procedure. Double revision of each member's outcomes was applied to ensure the validity and minimize the mistakes.

Table 1. Author, study type, year of publication, methodology and results

Author, year, country	Study type	Method	Outcomes
Pang, Xiao, et al. [9]	Review Article	2884 articles were retrieved from the databases, and 10 articles were included in the quantitative analysis	L-T4 administration at bedtime is as effective as administration before breakfast for patients with hypothyroidism.
Skelin et al. [10]	A three-period crossover randomized study	84 people with primary hypothyroidism were included in the study. They were assigned to each of three groups: timing regimen A (half an hour before breakfast), timing regimen B (an hour before the main meal of the day), and timing regimen C (at bedtime) (minimally 2 h after dinner).	The three investigated timing regimens of LT4 administration were equally efficient
Jawad et al. [11]	A prospective study	82 patients were included in the study. 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.	There were no differences between the morning and evening treatment with L-thyroxine on early normalization of TSH and FT4.
Shahram et al. [12]	A prospective, randomized, double-blind, cross-over placebo-controlled study	The sample involved 50 hypothyroidism patients aged 18 to 75 years old, who were randomly assigned to one of two classes. Per participant got two blind tablets a day (one levothyroxine tablet and one placebo tablet) before breakfast and dinner.	The clinical effectiveness of levothyroxine was decreased minimally when the administration duration was changed from before breakfast to before dinner.
Geer et al. [13]	Review article	A literature search identified four published studies of bedtime levothyroxine dosing.	For hypothyroid patients who choose not to take their drug with meals, bedtime administration of levothyroxine is an alternative.
Perez CL et al. [14]	A prospective, randomized, open-label, crossover study	This research, conducted in Brazil, involved 45 patients with hypothyroidism and a typical TSH level on levothyroxine therapy.	Absorption of levothyroxine is decreased when taking the hormone with breakfast.

Author, year, country	Study type	Method	Outcomes
Rajput et al. [15]	A prospective study	152 drug-free primary hypothyroid patients were split into morning (Group 1) and evening (Group 2) dosing groups and assessed for changes in biochemical composition, physical functioning, and Quality of Life over the span of 12 weeks.	Evening dose is as efficacious as morning dose and provides an alternate dosing regimen.
Bolk et al. [16]	A Randomized Double-blind Crossover Trial	105 patients with primary hypothyroidism were advised to take 1 capsule in the morning and 1 capsule at bedtime for 6 months (one containing levothyroxine and the other a placebo), with a 3-month transfer.	Thyroid hormone levels were greatly increased by taking levothyroxine at bedtime. Clinicians should think about administering levothyroxine at bedtime.
Bach-Huynh et al. [17]	Randomized Controlled Trial	TSH levels were measured in 65 adults with primary hypothyroidism who had been on stable levothyroxine dosages for at least six months. All patients received each levothyroxine regimen for eight weeks.	When compared to before-breakfast (fasting) administration, bedtime administration resulted in significantly higher mean TSH levels, but breakfast (nonfasting) administration resulted in significantly lower mean TSH levels.
Bolk et al. [18]	A pilot-study	The research involved 12 women who were taking l-thyroxine for primary hypothyroidism. Patients were studied twice: once while on a consistent morning thyroxine regimen and then two months later after transitioning to night-time thyroxine at the same dosage. Patients were hospitalized for 24 hours on each occasion, and serial blood samples were taken.	The results are better illustrated by increased gastrointestinal absorption of l-thyroxine at night.
Elliott [19]	Retrospective chart review	15 nursing home residents consuming levothyroxine during the change in administration period, with a mean age of 84 years, met inclusion requirements, with at least one serum TSH concentration recorded prior to and at least one serum TSH concentration reported after the change in administration time to midnight.	levothyroxine could be routinely administered after breakfast

3. RESULTS

The search of the mentioned databases returned a total of 107 studies that were included for title screening. 94 of them were included for abstract screening, which lead to the exclusion of 33 articles. The remaining 61 publications full-texts were reviewed. The full-text revision lead to the exclusion of 50 studies, and 11 were enrolled for final data extraction. The included studies had different study designs.

Pang, Xiao, et al. found that; in hypothyroid patients, the role of L-T4 administration before breakfast versus administration at bedtime had no statistically meaningful interaction with hormone thyrotropin (TSH) (Standardized Mean Differences (SMD) = 0.09, 95 percent confidence intervals) or free triiodothyronine (FT3). However, the FT4 level outcome was favorable for the L-T4 bedtime administration community [9].

Jawad et al. (2016), stated that there were no differences between the morning and evening treatment with L-thyroxine on early normalization of TSH and FT4 [11].

Perez CL et al. discovered that levothyroxine administration with breakfast increased TSH levels (2.89 vs. 1.9 mIU/L, $p=0.028$). Uncontrolled hypothyroidism (TSH 3.5 mIU/L) existed independently of levothyroxine form ($p=0.26$). There were no risk factors reported for TSH elevation [14].

Bolk et al. observed the effects of levothyroxine administration time (morning vs evening) on serum levels of TSH and T4 in 12 female patients for 4 months and discovered that administration of levothyroxine in the evening resulted in lower serum levels of TSH [16]. Later, in a larger trial by Bolk et al., 105 patients were observed for 6 months with a change in levothyroxine administration time from morning to evening, and the findings indicated better absorption for levothyroxine, reduced serum levels of TSH, and improved levels of T4 when levothyroxine was administered at night time [18].

Shahram et al. reported that; changing the timing of levothyroxine administration resulted in a 1.470.51 IU/mL rise in TSH ($P=0.001$) and a 0.351.05g/dL decrease in T4 ($P=0.3$) [12].

Rajput, Rajesh et al. reported that; at 6 and 12 weeks, there was no substantial change in

thyroid profile between the morning and evening dosage groups. In both classes, a similar dose of levothyroxine was needed to achieve euthyroidism. Though the evening group saw an earlier return of euthyroidism, the differential as compared to the morning group was not statistically important. [15].

Elliott, D P. observed that; since shifting the administration deadline to midnight, there was a 0.286 +/- 1.722 mU/mL (mean +/- SD) drop in serum TSH that was not statistically important ($t = 0.643$; $p = 0.532$). [19].

Geer et al. reported significant decrease in thyroid-stimulating hormone (TSH) levels with levothyroxine administration at bedtime versus 30 minutes before breakfast, one study found an increase in TSH when levothyroxine was taken at bedtime versus one hour before breakfast, and one study found no significant differences in TSH levels or other thyroid function monitoring limitations [13].

Bach-Huynh et al. reported that; Bedtime administration resulted in significantly higher mean TSH levels compared with before-breakfast (fasting) administration (2.19 mIU per L vs. 1.06 mIU per L; $P < .001$), but significantly lower mean TSH levels compared with breakfast (non-fasting) administration (2.19 mIU per L vs. 2.93 mIU per L; $P = .026$). Changes to meal timing, medication compliance, or levothyroxine timing occurred at a rate of 1.2% [17].

4. DISCUSSION

L-thyroxine (L-T4) has been considered the standard of care for the treatment of hypothyroidism for many years. This treatment is efficacious when administered orally, has a long serum half-life that permits daily administration, and results in resolution of the signs and symptoms of hypothyroidism in the majority of patients. The effectiveness of levothyroxine for reducing TSH levels is most dependent on the timing of meals in relation to drug administration [9].

Recently, some studies have been conducted in which the efficacy of L-T4 administration before breakfast and at bedtime was compared. The American Thyroid Association (ATA) recommends that, if possible, L-T4 be consistently taken either 60 minutes before breakfast or at bedtime (3 or more hours after the

evening meal), for optimal, consistent absorption [9].

Apaydin et al. [20] observed no significant differences in TSH and FT3 levels when L₄T₄ administration at bedtime was compared to administration before breakfast. However, a significant increase in FT4 level was observed in the bedtime group. This findings was consistent with findings of Bach-Huynh et al. [17].

Rajput et al. [15] discovered that the two administration periods were equally successful, which defied the findings of Bolk et al. [16,18]. This discrepancy may be attributed, in part, to differences in diet regimens and the impact of food consumption on levothyroxine absorption and oral bioavailability. Data from a major European population screening showed the impact of dietary iodine consumption on the epidemiology of thyroid dysfunction [21].

Patient adherence to their routine may have influenced TSH concentrations. Fasting can be less convenient and correlated with less consistent compliance. In a real-life setting, there could be less variation in TSH heterogeneity between regimens.

As a consequence, the findings of Elliott et al. [19], Bach-Huynh et al. [17] and Bolk et al. [18] studies could be congruent. According to Bartalena et al., the largest difference in serum TSH concentrations occurs when levothyroxine is administered early in the morning or late in the evening [22]. Furthermore, Persani et al. [23] demonstrated that TSH bioactivity varies with time of day, with fewer bioactive and differently glycosylated TSH molecules secreted at night. These results have significant clinical implications in our research because blood sampling for thyroid hormone analysis should also be performed in the morning as is currently done, even though the patient is taking levothyroxine as an evening dose.

5. CONCLUSION

There is conflicting data regarding effectiveness of morning dose versus evening dose in management of levothyroxine. The most recent evidences recommended that, if possible, L₄T₄ be consistently taken either 60 minutes before breakfast or at bedtime (3 or more hours after the evening meal), for optimal, consistent absorption.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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