TSH levels are altered by the timing of levothyroxine administration


SUMMARY

BACKGROUND Levothyroxine (L-T4) has a narrow therapeutic index, which is influenced by intestinal absorption. Administration with food, other medications, and even certain beverages such as coffee may result in interference with L-T4 absorption. The aim of this study was to determine whether taking L-T4 with breakfast or at bedtime results in significant elevations in serum thyrotropin (TSH) as compared with its traditional administration after an overnight fast, 1 hour before breakfast.

METHODS The study subjects were patients 18 to 75 years of age who had hypothyroidism for at least 2 years or had thyroid cancer with no evidence of persistent disease. The patients with hypothyroidism were required to have a stable TSH for >6 months while taking one of the two most popular brands of L-T4. Those with thyroid cancer were required to have a TSH level ranging from 0.01 to 0.5 μIU/ml. Patients were excluded from the study if they were pregnant, were taking medications known to interfere with L-T4 absorption or metabolism, or had a chronic illness such as heart disease, diabetes, or pulmonary, gastrointestinal, or renal disease.

At entry into the study, blood was drawn at 8 a.m. under fasting conditions to measure serum TSH, free thyroxine (T4), and total triiodothyronine (T3). Patients then completed three 8-week regimens defined by the timing of L-T4 administration. In one 8-week block, patients were asked to take L-T4 after an overnight fast at least 1 hour before breakfast (BB). In another 8-week block, patients were asked to take L-T4 with breakfast (WB), and in the last 8-week block, they were asked to take L-T4 as they retired for bed at least 2 hours after their last meal of the day (HS). Thyroid-function studies were repeated upon completion of each of the three regimens. Blood was separated into two aliquots, one for immediate processing for the thyroid-function studies and another for storage and processing by the General Clinical Research Center upon completion of the study. When patients were on one of the two morning regimens, L-T4 administration was delayed until after the phlebotomy.

Patients were asked to keep a diary on the time L-T4 was ingested and the times that foods were consumed at meals. They also were asked to take calcium supplements, ferrous sulfate, and multivitamins with a meal other than breakfast and separated from L-T4 by at least 4 hours. Telephone or e-mail follow-ups were made every four weeks.

Power calculations for the study that were performed to determine the sufficient sample size found that a sample of 42 patients would be sufficient to detect a 1.0 μIU/ml difference in TSH between the regimens with 90% power. Upon completion of WB or HS regimens, a rise in the serum TSH of ≥1.0 μIU/ml above the cohort’s mean TSH concentration during the fasting regimen was considered a treatment failure.

RESULTS Sixty-five patients completed the study; 42 had hypothyroidism and 23 had thyroid cancer. At the time of the baseline TSH determination, 88% of patients were taking their L-T4 in the fasting state, 9% were taking L-T4 at bedtime, and 3% were taking it at least an hour before breakfast.

![Figure 1](https://example.com/figure1.png)

**Figure 1.** This figure shows how the timing of L-T4 ingestion affects the mean serum TSH concentration. For the patients with hypothyroidism, Mean TSH was significantly higher in the WB group than in the BB group (3.74 vs 2.79 μIU/ml, P<0.001). Likewise, the mean TSH in the HS group was significantly higher than in the BB group (2.79 vs 1.54 μIU/ml, P<0.001). Finally, the mean TSH levels in the WB group were significantly higher than in the HS group (3.74 vs 2.79 μIU/ml, P = 0.0258).

![Figure 2](https://example.com/figure2.png)

**Figure 2.** This figure shows the effect of the timing of levothyroxine ingestion on the least squares means for serum LT4 concentrations for all patients combined (hypothyroidism and thyroid cancer). The LT4 concentrations were significantly lower during the “with breakfast” regimen than either the “before breakfast” regimen (1.24 vs. 2.35 ng/dL) *P or the “bedtime (HS) regimen *P<0.001).
The patients who declined to enter the study and those who withdrew from the study were similar in terms of age, sex, and L-T₄ dose as compared with patients who completed the study. The majority of patients without thyroid cancer had Hashimoto’s thyroiditis (73%) followed by postsurgical hypothyroidism (17%), and radioiodine-induced hypothyroidism (10%). The patients with thyroid cancer had a higher mean L-T₄ dose and a lower serum TSH at baseline than did those with hypothyroidism.

Protocol deviations were discovered at a rate of 1.2%; only 70% of patients completed the study diaries.

The cause of the thyroid failure (hypothyroid vs. thyroid cancer) had no significant effect on the differences in thyroid-function tests during the various timing regimens. Significant overlap was found between the baseline serum TSH and the mean values in the BB group (Figure 1). For the patients with hypothyroidism, the mean TSH in the WB group was significantly higher than in the BB group (3.74 vs. 1.54 μIU/ml, P<0.001). Likewise, the mean TSH in the HS group was significantly higher than in the BB group (2.79 vs. 1.54 μIU/ml, P<0.001). Lastly, the mean TSH levels in the WB group were significantly higher than in the HS group (3.74 vs. 2.79 μIU/ml, P = 0.0258) (Figure 1).

The free T₄ values were significantly lower in the WB group than in the BB group (1.16 vs. 1.23 ng/dl, P<0.001) or the HS group (1.24 vs. 1.34 ng/dl, P<0.001) (Figure 2). The total T₃ levels were not significantly different across the three groups (Figure 3).

Patients in the WB regimen had the greatest interindividual variability in serum TSH values; the HS measurements showed intermediate variability. An increase in serum TSH of >1 μIU/ml occurred in 55% of patients in the WB group, as compared with the BB group. Only 35% of patients had a rise in TSH of >1 μIU/ml upon completion of the HS regimen as compared with BB values.

**CONCLUSION** Administration of levothyroxine with breakfast or at bedtime is associated with greater variability and higher values of serum TSH as compared with taking it in a fasting state.

**COMMENTARY**

Levothyroxine is a routinely prescribed medication, but ensuring proper dosing can be an intricate process. Because levothyroxine has a very narrow therapeutic index, the margin between overdosing and underdosing can be quite small. In addition, absorption of this medicine is highly variable, depending on how it is taken. It has long been recognized that absorption of L-T₄ is reduced by concurrent ingestion of food (1). Likewise, simultaneous ingestion with certain medications may reduce the absorption of L-T₄; moreover, the list of offenders continues to grow (2,3). Multiple medical conditions, including nephrotic syndrome (4), malabsorption syndromes (5), and gastric acid hyposecretion (6) may also result in increased L-T₄ requirements. Recognition of the tendency for poor enteral absorption of L-T₄ has led clinicians to recommend taking it on an empty stomach and apart from other medications. The exact length of time needed to elapse before eating or taking other medications is not known; however, it is generally recommended that patients wait at least 30 to 60 minutes. For some patients, the ideal scenario of taking L-T₄ on an empty stomach at least 30 minutes before eating breakfast or taking other medications may be difficult to accommodate, particularly when other medications require similarly restrictive timing considerations.

The study by Bach-Huynh et al. was aimed at quantifying the changes in serum TSH levels with the administration of L-T₄ at various times to determine whether rigid timing is truly warranted. In this crossover trial, each patient served as her or his own control. It was surprising neither that the serum TSH went up when patients took their L-T₄ with breakfast nor that the fluctuations in thyroid-function tests were greatest in this group. Although a similar rise in serum TSH was also seen with administration of L-T₄ at bedtime as compared with the fasting regimen, this trend was less severe than that which occurred with breakfast. The authors verified that the current recommendations of taking L-T₄ on an empty stomach at least an hour before breakfast is the optimal condition for absorption of the drug. If this is inconvenient for patients, then taking L-T₄ at bedtime is a reasonable alternative, with the caveat that the patient may require slightly higher doses of L-T₄.

Bolk et al. (7) recently studied 12 patients with hypothyroidism taking L-T₄ during two 2-month regimens, one on a stable morning regimen of L-T₄ administration and the other after switching to nighttime administration using the same dose of L-T₄. After the conclusion of each study period, patients were admitted to the hospital, where serial blood samples were obtained via an indwelling catheter at hourly intervals for 24 hours. The study found that serum TSH levels were lower when the patients were given the L-T₄ at bedtime. Although seemingly at odds with the results of the study by Bach-Huynh et al., the findings of the two studies may in fact corroborate each other. For instance, in the Bolk study (7), patients waited only 30 minutes in the morning, but this may represent a midway point between the
two morning regimens used in the two studies. Taken together, these findings suggest that waiting longer than 30 minutes to eat before taking L-T4 may be necessary to avoid interference with L-T4 absorption.

The results of the elegant study by Bach-Huynh et al. confirm that L-T4 therapy is highly susceptible to interference of absorption in the presence of food and that TSH levels are more variable in this setting. Therefore, careful patient education regarding timing of administration with regard to food and other medications is essential before initiating levothyroxine therapy in order to achieve consistent TSH levels within the target range.

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References