TSH levels are altered by the timing of levothyroxine administration

Bach-Huynh TG, Nayak B, Loh J, Soldin S, Jonklaas J. Timing of levothyroxine administration affects serum thyrotropin concentration. J Clin Endocrinol Metab 2009; July 7, jc.2009-0860 [pii];10.1210/jc.2009-0860 [doi]

SUMMARY

BACKGROUND Levothyroxine (L-T_4) 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-T_4 absorption. The aim of this study was to determine whether taking L-T_4 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-T_4. 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-T_4 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 (T_4), and total triiodothyronine (T_3). Patients then completed three 8-week regimens defined by the timing of L-T_4 administration. In one 8-week block, patients were asked to take L-T_4 after an overnight fast at least 1 hour before breakfast (BB). In another 8-week block, patients were asked to take L-T_4 with breakfast (WB), and in the last 8-week block, they were asked to take L-T_4 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-T_4 administration was delayed until after the phlebotomy.

Patients were asked to keep a diary on the time L-T_4 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-T_4 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-T_4 in the fasting state, 9% were taking L-T_4 at bedtime, and 3% were taking it at least an hour before breakfast.

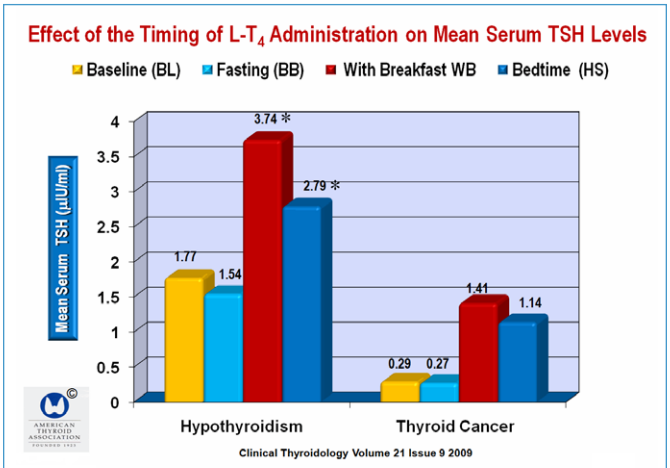

Figure 1. This figure shows how the timing of L-T_4 ingestion affects the mean serum TSH concentration. The serum TSH levels were significantly lower in the thyroid cancer group than in the group with hypothyroidism. For the patients with hypothyroidism, Mean TSH was significantly higher in the WB group 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). 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).

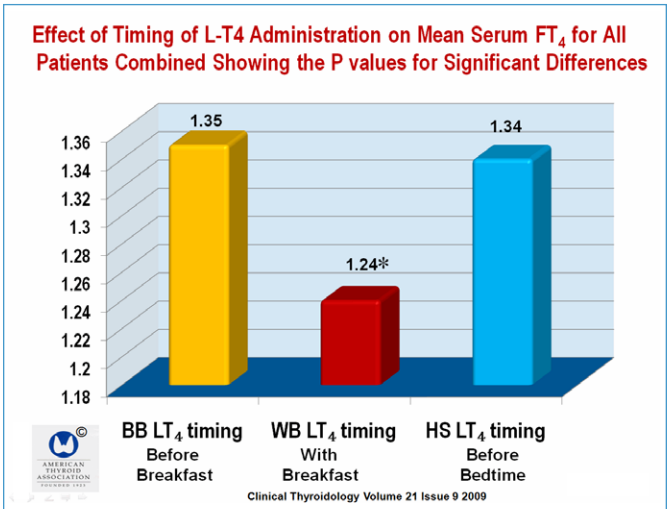

Figure 2. This figure shows the effect of the timing of levothyroxine ingestion on the least squares means for serum LT_4 concentrations for all patients combined (hypothyroidism and thyroid cancer). The FT_4 concentrations were significantly lower during the "with breakfast" regimen than either the "before breakfast" regimen (1.24 vs. 2.35 ng/dL) *P or the "bedtime (HS) regimen *P<0.001).

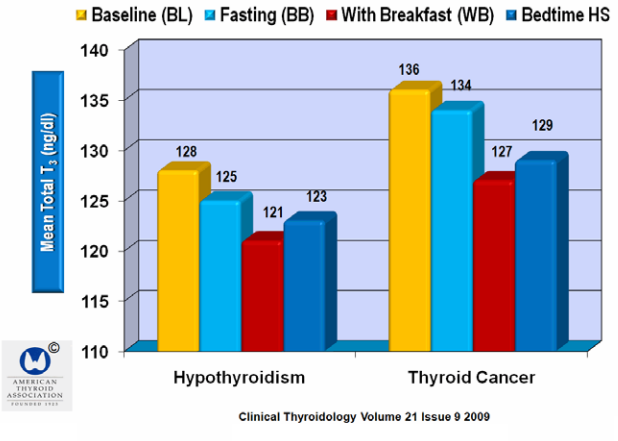

Figure 3. This figure shows the total T_3 levels were not significantly different across the three groups.

The patients who declined to enter the study and those who withdrew from the study were similar in terms of age, sex, and L-T_4 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-T_4 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 T_4 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 T_3 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-T_4 is reduced by concurrent ingestion of food (1). Likewise, simultaneous ingestion with certain medications may reduce the absorption of L-T_4; 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-T_4 requirements. Recognition of the tendency for poor enteral absorption of L-T_4 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-T_4on 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-T_4 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-T_4 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-T_4 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-T_4 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-T_4 at bedtime is a reasonable alternative, with the caveat that the patient may require slightly higher doses of L-T_4.

Bolk et al. (7) recently studied 12 patients with hypothyroidism taking L-T_4 during two 2-month regimens, one on a stable morning regimen of L-T_4 administration and the other after switching to nighttime administration using the same dose of L-T_4. 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-T_4 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-T_4 may be necessary to avoid interference with L-T_4 absorption.

The results of the elegant study by Bach-Huynh et al. confirm that L-T_4 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

1. Wenzel KW, Kirschsieper HE. Aspects of the absorption of oral L-thyroxine in normal man. Metabolism 1977;26:1-8.

2. Sachmechi I, Reich DM, Aninyei M, et al. Effect of proton pump inhibitors on serum thyroid-stimulating hormone level in euthyroid patients treated with levothyroxine for hypothyroidism. Endocr Pract 2007;13:345-9.

3. John-Kalarickal J, Pearlman G, Carlson HE. New medications which decrease levothyroxine absorption. Thyroid 2007;17:763-5.

4. Collins MT, Remaley AT, Csako G, et al. Increased levothyroxine requirements presenting as "inappropriate" TSH secretion syndrome in a patient with nephrotic syndrome. J Endocrinol Invest 2000;23:383-92.

5. Azizi F, Belur R, Albano J. Malabsorption of thyroid hormones after jejunoileal bypass for obesity. Ann Intern Med 1979;90:941-2.

6. Centanni M, Gargano L, Canettieri G. et al. Thyroxine in goiter, Helicobacter pylori infection, and chronic gastritis. N Engl J Med 2006;354:1787-95.

7. Bolk N, Visser TJ, Kalsbeek A, et al. Effects of evening vs morning thyroxine ingestion on serum thyroid hormone profiles in hypothyroid patients. Clin Endocrinol (Oxf) 2007;66:43-8.