Levothyroxine Dosing: Morning, Night, or In Between?

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Levothyroxine, the synthetic form of thyroxine, is routinely used as the primary form of thyroid hormone replacement in the management of hypothyroidism, a condition that affects up to 7% of the general population.[1] In 2017, levothyroxine was the most commonly prescribed medication in the United States, surpassing those used for diabetes, blood pressure, and heart disease.[2]

Levothyroxine use is monitored with thyroid blood tests, the results of which depend partly on the stability of circulating thyroid hormone levels after oral ingestion. Fluctuating thyroid test results require more frequent adjustments in levothyroxine dose. In turn, constantly adjusting a patient's levothyroxine dose requires greater follow-up monitoring, which is associated with increased use of healthcare resources, higher costs, and lost economic productivity due to lost time and wages.[3]

Thus, there has been substantial interest in ensuring that patients are given the appropriate instructions for taking their levothyroxine, to allow the medication to be absorbed as consistently as possible.

Current Guidelines

Levothyroxine is absorbed in the small intestine and is 70%-80% bioavailable in the euthyroid individual.[4] Peak absorption is achieved at approximately 2 hours after oral ingestion but can be delayed to 3-4 hours if it is ingested simultaneously with interfering medications, supplements, or some foods/drinks.[4]

As such, current guidelines by the American Thyroid Association advise patients to take levothyroxine at least 60 minutes before the first meal of the day or at bedtime (at least 3 hours after the evening meal), and at least 4 hours apart from other medications or supplements, if possible.[5]

Substances That Block Absorption

Studies of solid levothyroxine tablets have reported that less is absorbed when it is taken concurrently with substances that include coffee,[6] soy,[7] calcium carbonate,[8,9] iron,[10] aluminum hydroxide,[11] sucralfate,[12,13] cholestyramine,[14] colesevelam,[15] raloxifene,[16] orlistat,[17] phosphate binders,[18] or cow's milk,[19] compared with when levothyroxine is taken alone.

It is thought that interference occurs as a result of physical adsorption (complexing) between the interfering substance and levothyroxine in the gastrointestinal tract. These studies show that taking levothyroxine together with an interfering substance can decrease the amount of thyroid hormone that is absorbed by as much as 50%, although the degree of this interference has been variable.

One reason for this variability is that many of these studies were performed in nonrandomized, uncontrolled trials of relatively small cohorts. Some of these effects have been documented in individual case reports only.

Conditions That Affect Absorption

Certain conditions have the potential to further reduce the absorption of oral levothyroxine. If an individual has known *Helicobacter pylori*–related gastritis, atrophic gastritis, or celiac disease, a higher dose of levothyroxine may be needed to overcome these malabsorptive states.

Gastric bypass surgeries do not appear to have a substantial effect on levothyroxine requirements, as the ileum is the primary site of absorption for thyroid hormone. However, the dose of levothyroxine used (which is weight-based) should be monitored closely and probably decreased following bariatric surgery and ensuing weight loss.[20]

Contradictory Findings

Overall, the majority of studies demonstrate that oral levothyroxine tablets are best absorbed when they are taken on their own. In one trial,[21] 65 participants with hypothyroidism were randomly assigned to take their levothyroxine before breakfast (ie, in the fasting state), with breakfast, or at bedtime. Participants adhered to each of these three regimens for 8 weeks and completed all three regimens by the end of the 24-week total study period. Using the degree of serum TSH elevation as a marker of hypothyroidism (ie, the higher the TSH, the less levothyroxine is absorbed), the study reported that TSH levels were significantly higher when levothyroxine was taken with breakfast or at bedtime, versus when levothyroxine was taken in the fasting state.

However, other studies suggest the contrary—that interfering substances may not pose a significant problem. One study of 84

patients showed that thyroid function tests were similar whether levothyroxine was taken 30 minutes before breakfast, 1 hour before the main meal of the day, or at bedtime.[22]

Similarly, another report showed no difference in thyroid hormone levels whether levothyroxine was taken before breakfast or at bedtime in children.[23] Furthermore, a study in the Netherlands showed that levothyroxine taken at bedtime actually resulted in greater thyroid hormone absorption and higher quality-of-life scores than in those who took levothyroxine in the morning.[24]

Absorption of Liquid and Gel Formulations

Orally administered liquid and soft gel levothyroxine formulations have been introduced in many countries over the past decade, including the United States. Because many of these formulations do not contain such common additives as dyes, sugars, glycerol, alcohol, lactose, and other fillers, they have the potential to be more quickly absorbed in the gastrointestinal tract, and the issue of interfering substances complexing with solid levothyroxine tablets or the presence of intestinal malabsorptive disorders may possibly be averted with their use.[25]

Indeed, several studies have reported that serum thyroid function test results were similar whether liquid levothyroxine or soft gel capsules were taken together with breakfast or up to 30 minutes before breakfast.[26-28]

In one meta-analysis of eight studies, serum TSH concentrations were generally lower with liquid versus tablet levothyroxine in patients with a gastrointestinal malabsorptive disorder, suggesting that the liquid formulation is able to overcome processes of impaired intestinal absorption.[29]

Concluding Thoughts

It makes sense to advise patients taking oral levothyroxine that their medication may not be fully absorbed if it is taken together with or very close in timing to certain substances. Patients should be counseled on the types of substances that can impair absorption while recognizing that this will not occur in all patients, even if levothyroxine and these substances are taken concurrently.

Perhaps most important to remember is that some patients take their clinician's instructions quite literally. As such, practical considerations and attention to the overall patient should be kept in mind. I stress that setting an alarm to wake up in the middle of the night just to be able to take levothyroxine well before breakfast is disruptive to sleep and health, and that this should not be done.

If the patient's daily lifestyle and preference is to take the levothyroxine immediately upon waking, which is 30 minutes before breakfast, I would encourage this. However, this practice should be relatively consistent day to day, so that any potential malabsorption that occurs with breakfast occurs to a similar degree each day and can be overcome with a slightly higher levothyroxine dose as needed.

This practice would also pertain to patients who prefer taking their levothyroxine at bedtime. As long as the practice and the minimum time period after eating the last meal of the day are consistent, serum TSH concentrations would probably be relatively stable.

It is also important to clarify that a higher dose of levothyroxine is not necessarily harmful as long as serum thyroid hormone tests remain consistently at goal, whether that goal is TSH suppression in thyroid cancer patients or normal TSH levels in non-cancer patients.

Finally, there is a need for further research on the optimal timing of levothyroxine use. As the American Thyroid Association guidelines for hypothyroidism describe,[5] no long-term studies have examined patients' ability to adhere to the various timing regimens as recommended, the clinical outcomes of taking levothyroxine at different times of day, and the health effects of constantly varying serum TSH concentrations.

Dr Leung serves on the board of directors of the American Thyroid Association (ATA) and is editor-in-chief of Clinical Thyroidology*, one of the journals of the ATA.*

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