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# Advances in the Study of The Dosing Time of Thyroxine Tablets

**PENG Dongmei[1*] and DU Yonggang[2]**

[1]Day Surgery Center,West China Hospital of Sichuan University, Chengdu Sichuan 610041, China
[2]Department of gastrointestinal surgery, Pengzhou People's Hospital. Chengdu Sichuan 610000), China

[*]**Corresponding Author:**
PENG Dongmei, Day Surgery Center,West China Hospital of Sichuan University, Chengdu Sichuan 610041, China

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## 1. Abstract

Long-term thyroxine tablet administration is a common requirement for patients post-thyroidectomy. The conventional method involves fasting and oral administration of the tablets at least 30 minutes prior to breakfast. However, the optimal timing for drug administration remains a contentious issue, with emerging clinical research. The absorption of thyroxine tablets can be significantly influenced by traditional breakfast foods such as milk and soy milk, potentially compromising drug efficacy for patients unwilling to abandon these dietary habits. This review examines the in vivo absorption process of thyroxine tablets and their interaction with food. Findings suggest that the optimal timing for thyroxine tablet intake is either one hour prior to breakfast or before bedtime (at least three hours post-dinner). If the diet includes soy milk, milk, coffee, or high-calcium or high-iron foods, a minimum four-hour interval is recommended. Consequently, patients with poor compliance or a preference for traditional Chinese breakfast items such as milk and soy milk may consider bedtime medication.Levothyroxine tablets, a prevalent clinical preparation, are primarily utilized for hypothyroidism treatment and postoperative Thyroid-Stimulating Hormone (TSH) suppression therapy in differentiated thyroid cancer cases. As the most frequently administered drug in thyroid surgeries, most patients require lifelong consumption. The standard administration involves oral intake on an empty stomach in the morning, with a minimum of 30 minutes before consuming any food. Given that its absorption is significantly influenced by dietary intake, foods that interfere with its absorption should be avoided for breakfast. Moreover, a minimum interval of 4 hours is recommended between the consumption of soy milk, milk, and coffee. This administration protocol, however, is often inconvenient and results in poor patient compliance. Traditional breakfast habits, such as consuming soy milk or milk, are deeply ingrained in Chinese culture. Consequently, some patients are reluctant to alter these habits, inevitably impacting drug absorption and hindering the desired therapeutic effect. Although taking a small pill may seem trivial, it profoundly affects a patient's lifestyle habits. This article aims to address a common patient query regarding the flexibility of Levothyroxine tablet intake timing. It reviews the absorption process of Levothyroxine tablets in the body and their interaction with food, seeking a feasible alternative method.

## 2. Absorption of Thyroxine Tablets

### 2.1 Thyroxine Tablets Chemical Structure

Levothyroxine sodium tablets, a frequently employed clinical preparation, are chemically known as 4-oxygen - (4-hydroxy-3,5-diiodophenyl) -3,5-diiodo-L-tyrosine sodium,with a molecular formula of C15H10I4NNaO4•xH2O. This compound mirrors the thyroxine naturally secreted by the thyroid gland. It is metabolized into T3 in peripheral organs and exerts its specific effects by binding to the T3 receptor. The human body cannot differentiate between endogenous and exogenous thyroxine. Upon oral administration, the drug molecules dissociate under the influence of gastric acid and are subsequently absorbed in the intestine, primarily in the jejunum and ileum. The absorption rate is approximately 70%-80% [1-3], with a peak time around 5-6 hours.

### 2.2. Gastric Dissociation

The thyroxine tablet remains in the stomach for approximately 35 ± 30 minutes, during which drug molecule dissociation occurs. It then takes roughly 7±3 minutes to traverse the duodenum, with about 15±5% of the drug being absorbed. Subsequently, it enters the upper jejunum segment, remaining for about 31±8 minutes. The upper jejunum segment can absorb approximately 29±14% of the drug, while the lower jejunum segment can absorb around 24±11%[1].Gastric dissociation is a prerequisite for the absorption of thyroxine tablets. Research indicates that the dissociation rate of thyroxine tablets in the stomach exhibits a U-shaped alteration with the increase of gastric acid PH: at PH1-3, the dissociation rate gradually decreases, at PH3-7, the dissociation rate reaches its nadir, and at PH > 7, the dissociation rate progressively ascends[5]. The PH of human gastric acid is approximately 0.9-1.5, which can provide optimal dissociation conditions for thyroxine tablets. Some researchers have reported that when the PH is less than 2.4, the dissociation of thyroxine tablets can exceed 85% within 20 minutes[6]. Therefore, to ensure sufficient dissociation of thyroxine tablets, they should be taken on an empty stomach with a fasting period of at least 20 minutes.

### 2.3. Enteral Absorption

Thyroxine tablets, characterized by their amphoteric molecules, possess lipophilic aromatic rings and hydrophilic side chains. They contain three ionizable groups, including two acidic groups (hydroxyl and carboxyl) and one alkaline group (amino)[7]. The bipolarity of thyroxine tablets, coupled with the charge acquired post-dissociation, impedes its diffusion through the cell membrane. Consequently, without a specific carrier, thyroxine tablets are unable to traverse the lipid bilayer of the cell membrane[8].

## 3. Factors Affecting the Absorption of Thyroxine Tablets

### 3.1. Diseases Affecting the Absorption of Thyroxine Tablets

#### 3.1.1. Diseases Affecting the Gastric Dissociation of Thyroid Hormone Tablets

The demand for thyroid hormone increases with the increase of gastric pH (ρ=0.4229; p=0.0007). A multivariate analysis showed that, in addition to body mass index, gastric pH is a more important independent variable determining the effective dose of T4[11]. Therefore, decreased gastric acid secretion or elevated gastric acid pH may impact the intragastric dissociation of thyroxine tablets. Factors contributing to this include HP infection, chronic atrophic gastritis, major gastric resection, and gastric bypass surgery[9-12]. Poor intragastric dissociation of thyroxine tablets can affect subsequent absorption. Rapid gastric emptying, as seen in acute gastroenteritis, major gastrectomy, and gastric bypass surgery, can also lead to inadequate dissociation of thyroxine tablets. Patients with gastroparesis may require increased thyroxine tablet volume due to de-

layed gastric emptying [4].

### 3.2. Diseases Affecting Intestinal Absorption

Intestinal procedures and diseases that affect intestinal absorption, such as short bowel syndrome, celiac disease, lactose intolerance, inflammatory bowel disease, parasitic infections, and biliopancreatic shunts, can impair the absorption of thyroxine tablets [13-15]. A study reported that a patient who presented a marked malabsorption of LT4 without gastrointestinal malabsorptive disorder, a decreased membranous expression of LAT1 and LAT2 transporter in terminal ileum and ascending colon. But the author could not elucidate the direct relationship between LT4 absorption and transporter LAT1 and LAT2 in molecular levels[16].

### 3.3. Drugs Affecting the Absorption of Thyroxine Tablets

Certain pharmaceutical ingredients or excipients, such as calcium and iron supplements, alkaline antacids, and bile acid chelators, can bind to LT4 molecules and inhibit their transmembrane transport[17-20]. Proton pump inhibitors and H2 receptor antagonists can inhibit gastric acid secretion and affect the dissociation process of thyroxine tablets, leading to malabsorption[21-22]. Conversely, vitamin C has been shown to stimulate gastric acid secretion, promoting the dissociation of thyroxine tablets and improving absorption[48-49]. The LT4 molecule is transported by transmembrane proteins. Ciprofloxacin competitively inhibits the OATP1A2 transporter, thereby decreasing the absorption of thyroxine tablets[23]. Rifampicin, a well-known OATP inhibitor, has been hypothesized to decrease intestinal absorption of LT4[24]. Estrogens, rifampicin, raloxifene, and carbamazepine may elevate serum thyroxine-binding globulin, decrease free T3 and free T4, and cause hypothyroxinemia[24-25]. Conversely, androgens decrease TBG and lead to hyperthyroxinemia[26]. Drugs such as carbamazepine, fluoxetine, sertraline, sorafenib, and others reduce thyroxine levels in the body by converting T4 to bioactive hormones, T3, or other inactive metabolites[27-29].

### 3.4. Gut Microbiota Affecting the Absorption of Thyroxine Tablets

The gut microbiota plays a significant role in the body's homeostasis and the development of immune cells. Dysregulation of the gut microbiota can promote inflammation, decrease immune tolerance, damage the intestinal membrane, and increase intestinal permeability[30-31]. Additionally, the gut microbiota can directly affect thyroid hormone levels through its deiodinase activity and TSH inhibition[30]. The gut microbiota also influences the absorption of minerals important for the thyroid, including iodine, selenium, zinc, and iron[32]. Probiotics have been shown to reduce serum hormone fluctuations and have a positive effect on trace minerals such as selenium, zinc, and copper[33]. Knezevic J et al, [34]. considered that a strong thyroid–gut axis exists. It appears to display a not well known but important correlation regarding the effect of the gut bacteria on the immune system and thyroid function.

### 3.5. Foods That Affect the Absorption of Thyroxine Tablets

#### 3.5.1. Foods That Decrease the Absorption of Thyroxine

Numerous studies have since reported on foods that interfere with the absorption of thyroxine tablets, including soy milk, milk, coffee, cellulose, papaya, grapefruit juice, high-calcium foods, and iron-rich foods. Bell DS et al.[35] reported a decrease in thyroxine tablet absorption when consumed concurrently with soy protein. Similarly, Conrad SC et al.[36] found that soy formula impacted the absorption of thyroxine tablets in children with hypothyroidism. However, Gatta E et al, [37]. though that the inference of soy products on L-T4 absorption, if present, seems to have little clinical impact. Chon DA et al, [38].Studied the effects of consuming milk and thyroxine tablets together and found a reduction in thyroxine tablet absorption, potentially due to the influence of calcium, protein, and other nutrients. Benvenga S et al, [39].Conducted in vivo and in vitro studies on the simultaneous intake of coffee and thyroxine tablets. The in vivo studies revealed altered pharmacokinetics and a delayed peak time of serum T4, while the in vitro studies showed that coffee reduced the absorption of organic and inorganic substances, acting as a weak T4 chelator. Lai YW et al, [40].Found that tea, like coffee, significantly interfered with the absorption of thyroxine due to shared components such as caffeine, polyphenols, and polysaccharides. Liel et al,[41].Demonstrated the non-specific, dose-dependent adsorption of wheat bran to thyroxine in vitro. DeianaL et al,[42].Reported a case of a thyroidectomy patient who consumed large amounts of papaya, resulting in decreased T4 levels. After discontinuing papaya consumption, T4 levels increased. The authors suggested that papain could reduce histamine-induced gastric acid secretion, and papaya fiber could bind with T4, thus reducing the absorption of thyroxine tablets. Bailey DG et al,[43].Found that flavonoids such as hesperidin and naringin in orange juice and grapefruit juice could interfere with the transmembrane transporter OATP1A2 on small intestinal chion cells, potentially reducing the oral availability of transport substrates for 2-4h. Singh N et al, [44-45].Found that at PH 2.0, T4 would adsorb onto calcium carbonate, preventing its absorption at the intestinal level. They suggested that both acute and chronic intake of calcium carbonate would reduce the availability of T4. Campbell NR et al, [46].Confirmed in vitro that at PH < 7.4, one Fe2+ molecule could combine with three T4 molecules to form an insoluble complex, thereby reducing the absorption of thyroxine tablets.The 2006 ATA guide of Update of Newborn Screening and Therapy for Congenital Hypothyroidism[47] also clearly states that soy, iron, and calcium should be avoided. Zamfirescu et al, [18].Conducted a study to compare the absorption of levothyroxine when administered alone or in combination with calcium carbonate, calcium citrate, or calcium acetate, each containing 500 mg of elemental calcium, in 8 healthy adults with normal thyroid function. Serum thyroxine levels were measured every 6 hours after ingestion of the study drug. The results showed that taking thyroxine tablets together with the three calcium preparations mentioned above reduced the absorption rate by 20%-25%. Therefore, it is recommended to take them at least 4 hours apart.

### 2.42 Foods that increase the absorption of thyroxine tablets

Jubiz W et al, [49].Conducted a study on 31 patients with hypothyroidism for 3 cycles, with each cycle lasting 2 months. In the first and third cycles, patients were given thyroxine tablets alone, while in the second cycle, patients were given thyroxine tablets with 120ml of water containing 500 mg of to swallow the same amount. Serum concentrations of free T4 and TSH were measured at the end of each cycle. The results showed that in patients with hypothyroidism and gastrointestinal diseases, serum concentrations of TSH and free T4 improved after taking vitamin C. This improvement may be related to the increased solubility of thyroxine in the stomach. Skelin et al.[15] also suggested that this improvement could be associated with the ability of vitamin C to reduce stomach acid. The study by Ant´unez et al.[48] also supports the view that vitamin C can promote the absorption of thyroxine tablets. Gezer E et al[50]. Reported that the significant positive effect of morning exercise on the absorption of LT4 tablets.

### 3.2. Dosing Time of Thyroxine Tablets

As early as 1977, Wenzel KW et al, [3].Administered 100ug of thyroxine tablets orally to patients using an isotope method. They found that the absorption rate of thyroxine tablets in a fasting state was approximately 79.3±7.2%, while in a fed state, it was about 63.9±10.5%. This finding further substantiated the recommendation for thyroxine tablets to be taken on an empty stomach. Perez CL et al, [51].Conducted a prospective, randomized controlled study in which 45 patients with primary hypothyroidism treated with levothyroxine were randomly assigned to a levothyroxine administration regimen for 90 days (fasting or at breakfast). Clinical and biochemical analyses were performed before administration and on days 45, 90, 135, and 180, mainly monitoring TSH levels. The results showed that TSH levels were higher when levothyroxine was administered at breakfast compared to fasting (2.89 vs. 1.9 mIU/L, p=0.028). They suggest that levothyroxine administration at breakfast may be an alternative for patients with compliance difficulties due to the need to delay intake. However, this approach is more likely to lead to variations in TSH levels, so patients need to be closely monitored. For patients who need to strictly control TSH levels, it is recommended to take levothyroxine when fasting.Similarly, Bach-Huynh TG et al, [52].Developed three dosing schedules: the first one was given after overnight fasting and at least 1 hour before breakfast, the second one was given before sleep and at least 2 hours after the last meal of the day, and the third one was given in the eating state and within 20 minutes after breakfast. Each plan

was performed for 8 weeks, totaling 24 weeks. The above three schemes were cross-combined, and 8 groups could be combined. They randomly assigned 65 patients who were receiving levothyroxine to the study. Thyroid function testing was conducted at the beginning of the study and at the end of every 8 weeks. They found that when levothyroxine was given in the fasting state, the average thyrotropin concentration was 1.06 ± 1.23 mIU/L. However, when levothyroxine was taken at breakfast, the serum thyrotropin concentration significantly increased (2.93 ± 3.29 mIU/L), and the serum TSH concentration also significantly increased (2.19 ± 2.66 mIU/L) when levothyroxine was taken before bed. In a study by Ala S. et al, [55], 50 patients with hypothyroidism were randomized into two groups. Each group blindly received two tablets (one levothyroxine tablet and one placebo tablet) daily before breakfast and before dinner. After two months, the groups exchanged dosing schedules and continued the new regimen for two months. Serum TSH and T4 levels were measured before and after treatment in each group. The results showed that changing the timing of pre-breakfast levothyroxine administration to pre-dinner resulted in an increase in TSH levels of 1.47±0.51 μIU/mL (P=0.001) and a decrease in T4 levels of 0.35±1.05 μg/dL (P=0.3). The authors concluded that changing the timing of levothyroxine administration to improve patient compliance would result in lower treatment outcomes.Bolk N et al, [53].Conducted a randomized, double-blind, cross-over trial involving 105 patients diagnosed with primary hypothyroidism. The patients were directed to consume one capsule on an empty stomach half an hour prior to breakfast and another capsule before retiring to bed in the evening for a duration of six months. Each capsule contained either levothyroxine or a placebo, and the patients were instructed to switch them after three months. The patients' thyroid hormone levels were monitored at the beginning of the trial and subsequently every six weeks. The findings indicated that the TSH level decreased by 1.25 mIU/L (95% confidence interval [CI], 0.60-1.89 mIU/L; P<0.001), the free T4 level increased by 0.07 ng/dL (0.02-0.13 ng/dL; P=0.01), and the total T3 level increased by 6.5 ng/dL (0.9-12.1 ng/dL; P=0.02) when levothyroxine was taken before sleep as compared to its intake before breakfast. The researchers concluded that taking levothyroxine before bed could significantly enhance thyroid hormone levels. In conclusion, the optimal times to consume thyroxine tablets are: one hour before breakfast, before bedtime, 30 minutes prior to meals, and during meals.The 2014 ATA Guidelines for the treatment of hypothyroidism[54] suggest that thyroxine tablets should be taken one hour before breakfast or before bed (three hours or more after dinner) and should be consumed at least four hours apart from foods that may interfere with their absorption. Rajput R et al, [56].Divided 152 patients with primary hypothyroidism who were not receiving medication into morning (group 1) and evening (group 2) dosing groups. They showed that at the end of 12 weeks, 70 subjects in group 1 (90.90%) and 72 subjects in group 2 (96%) achieved normal thyroid function. Clinical symptoms, total clinical scores, and thyroid status improved in both groups at 6 and 12 weeks (P value < .0001). Hence, they inferred that evening dose was as effective as morning dose in improving thyroid status, lowering total cholesterol levels, improving clinical signs and symptoms, and improving quality of life. Pang X et al, [57].Conducted a meta-analysis on the effect of pre-breakfast and bedtime administration of levothyroxine on hypothyroidism evidence. The analysis showed that for patients with hypothyroidism, bedtime administration of L-T4 was as effective as taking it before breakfast.

In addition, studies in pediatric and elderly patients have shown similar results. Navid A et al, [58].Categorized 84 hypothyroid children who were able to achieve clinically and biochemically normal thyroid function on early morning levothyroxine therapy into those who received levothyroxine at bedtime (group A) or those who continued to receive early morning levothyroxine intake (group B). The results showed no differences in mean serum concentrations of triiodothyronine, thyroxine, and thyrotropin at baseline, 3 months, and 6 months. Mean serum aspartate aminotransferase, alanine aminotransferase, creatinine, and lipid parameters remained similar in both groups. They concluded that intake of levothyroxine at bedtime has the same efficacy as intake of levothyroxine early in the morning in maintaining normal thyroid function in children with hypothyroidism. Similarly, Akın O et al, [59]after studying the time of administration of levothyroxine in 163 children with hypothyroidism, found that there was no difference in the use of bedtime or morning regimens in the first-treatment patients and the patients who had received treatment for a long period of time. For first-treatment patients, consideration of patients' preference for dosing time may increase their adherence to medication. Therefore, they suggested that the timing of drug administration should be chosen according to the patient's preference. de Mello RB et al, [60].Randomly assigned 201 patients with primary hypothyroidism aged ≥60 years who had been treated with LT4 for at least 6 months and had received a stable dose for at least 3 months to either a morning LT4 intake (60 min before breakfast) or a bedtime LT4 intake (60 min after the last meal) initiation group. After ≥12 weeks of follow-up, the dosing regimens were exchanged. Results showed mean TSH levels of 2.95 ± 2.86 in the morning group and 3.64 ± 2.86 in the bedtime group, p = 0.107. They concluded that although older adults have a high prevalence of oral underlying disease and take a variety of medications, in the case of LT4, regardless of the treatment regimen (morning or bedtime), thyroid-stimulating hormone levels and the frequency of controlled hypothyroidism were similar during the follow-up period. Frequency was similar.Therefore, for patients with poor adherence and unable to ensure that the drug is taken on an empty stomach in the early morning, bedtime administration may also be considered[61]. However, intestinal peristalsis is reduced at night, and taking thyroxine tablets before bedtime will lead to prolonged exposure of the drug to the intestinal mucosa[62]. Additionally, basal gastric acid secretion is increased at night to reach the peak of the diurnal rhythm[63], which may result in an increase in the rate of absorption. Some patients may suffer from symptoms such as cardiac tachycardia and euphoria and have difficulty sleeping. The dosage of the medication still needs to be adjusted on an individualized basis.

## 4. New Thyroxine Formulations

As some common gastrointestinal disorders and the use of interfering medications and foods may lead to poor control in a large number of patients with the expected dose of thyroxine, some novel agents are emerging[64].

### 4.1. Liquid Formulation

This formulation dissolves levothyroxine sodium in ethanol and glycerol and has been shown to be bioequivalent to conventional formulations[65].The liquid preparation does not require an acid gastric environment. Many pharmacokinetic studies demonstrated a more rapid absorption for the liquid L-T4, or capsule, than with tablet[66]. Further studies have supported the lower susceptibility of liquid formulations to food interference[67]. Liquid formulations have also been suggested to offer superior performance to T4 tablets in patients with H. pylori infection, atrophic gastritis, lactose intolerance, cirrhosis, those infected with Giardia intestinalis, and those who have undergone bariatric surgery[70-75]. Additionally, this liquid formulation has been shown to overcome the coexisting effects of proton pump inhibitors[76], calcium and iron supplements[77-78], aluminum/magnesium hydroxide, sodium alginate, aluminum hydroxide, sodium alginate, and sevelamer[79]. Liquid L-T4 can be given to patients unable to swallow capsules or tablets, and this is one of its major benefits[80]. Furthermore, liquid formulations are also expected to treat some refractory hypothyroidism by sublingual route of administration[81]. Moreover, liquid thyroxine may be able to be ingested with breakfast[68-69]. Liquid LT4 seems to be equally effective when taken before or during breakfast. The drug efficacy analysis of specific populations, including newborns, pregnant women, and the elderly, confirms the high value and safety of liquid LT4[82].

### 4.2. Soft Gel Capsules

In liquid gel cap form, levothyroxine sodium is dissolved in water and glycerol and then placed in a gelatin matrix to prevent degradation of the active ingredient. Softgel formulations dissolve better than tablet formulations at different media pH values[83]. Similar to liquid capsules, softgel capsules have been shown to be bioequivalent to tablet thyroxine[84] and more effective in the treatment of patients suffering from gastric disorders[85]. The effectiveness of softgels also appears to be less sensitive to nutrient interference, and similarly, studies have reported that softgels can be taken with breakfast[86].Poorly controlled hypothyroidism, sometimes termed refractory hypothyroidism. For these patients, optimization of ingestion routines and alternative formulations and routes of administration of LT4 can be considered, including oral liquid, intrave-

nous, intramuscular, and even rectal formulations[87].In addition, Opazo MC et al. reported that utilizing CO2 nanobubbles could enhance T4 bioavailability and cell permeability, leading to more efficient transport into cells[88]. Ducharme M et al, [89]. Reported that a new oral solution of LT4 (manufactured by IBSA, Institut Biochimique SA) has been recently approved and commercialized under the name Tirosint®-SOL (including Tirosintsol, Tirosint Solution, Syntroxine Sol, Levotirsol, Synotirex, Tirosol, Solsint, and Tsoludose) Results in Similar Bioavailability Whether Taken 30 or Just 15 Minutes Before a High-Fat High-Calorie Meal.

## 5. Conclusion

The best time to take thyroxine tablets should be 1 hour before breakfast or before bedtime (3 hours and more after dinner). Breakfast should try to avoid choosing food that affects the absorption of thyroxine tablets, such as consuming soymilk, milk, coffee, high-calcium or high-iron foods. The interval should be more than 4 hours. At present, domestic administration generally follows the drug instructions, instructing patients to take the drug early in the morning on an empty stomach, 30 minutes before breakfast. According to the discussion of the previous study, if the patient's compliance is poor or preference for milk, soybean milk, and other traditional habits of the Chinese breakfast, then the drug can be considered to be given before bedtime. Considering the possible factors affecting gastric emptying, the absorption of thyroxine tablets is better when the drug is taken 3 hours or more after dinner, and no more food should be taken after the drug is taken until the next morning. In addition, newer formulations are good options but are still not widely used.

## References


1. Hays MT. Localization of human thyroxine absorption. Thyroid. 1991;1(3): 241- 248.
2. Hays MT. Absorption of oral thyroxine in man. J Clin Endocrinol Metab.1968; 28(6): 749-756.
3. Wenzel KW, Kirschsieper HE. Aspects of the absorption of oral L-thyroxine in normal man. Metabolism. 1977; 26(1): 1-8.
4. O S K, M M AM, A N P. Gastroparesis - a novel cause of persistent thyroid stimulating hormone elevation in hypothyroidism. J La State Med Soc. 2015; 167(2): 47-9.
5. Won CM. Kinetics of degradation of levothyroxine in aqueous solution and in solid state. Pharm Res. 1992; 9(1): 131-137.
6. Benet LZ. The role of BCS (biopharmaceutics classification system) and BDDCS (biopharmaceutics drug disposition classification system) in drug development[J]. J Pharm Sci. 2013; 102(1): 34-42.
7. Toth G, Maz´ak K, Hosztafi S. Species-specific lipophilicity of thyroid hormonesand their precursors in view of their membrane transport properties. J Pharm Biomed Anal. 2013; 76: 112-118.
8. Virili C, Antonelli A, Santaguida MG,Benvenga S, Centanni M.Gastrointestinal Malabsorption of Thyroxine. Endocr Rev.2019; 40(1)118-136.
9. Trimboli P, Ossola N, Torre A,Mongelli F, Quarenghi M, Camponovo C, et al. The performance of levothyroxine tablet is impaired by bariatric surgery. Endocrine. 2023;80(3):563-569.
10. Jamil MZZ Sr, Salman S, Akhtar M, Iqbal S, Bhalli A, Farooq H, et al. Determining the Association Between Helicobacter Pylori Infection and Treatment-Refractory Hypothyroidism. Cureus. 2022;14(1): e21316.
11. Virili C, Bruno G, Santaguida MG, Gargano L, Stramazzo I,Vito CD, et al. Levothyroxine treatment and gastric juice pH in humans: the proof of concept. Endocrine. 2022;77(1):102-111.
12. Subramaniam K, Babu T, Sreevalsan KC, Mathew S. Levothyroxine Absorption Test - Results and Follow Up of Patients from a Single Center. Indian J Endocrinol Metab. 2023;27(1):32-36.
13. Lebwohl B, Sanders DS, Green PHR. Coeliac disease. Lancet. 2018;391(10115):70-81.
14. Virili C, Stramazzo I, Santaguida MG,Bruno G, Brusca N, Capriello S, et al. Ulcerative Colitis as a Novel Cause of Increased Need for Levothyroxine. Front Endocrinol (Lausanne). 2019; 10:233.
15. Skelin M, Lucijanić T, Amidžić Klarić D,Rešić A, Bakula M, Čizmek AML, et al. Factors Affecting Gastrointestinal Absorption of Levothyroxine: A Review. Clin Ther. 2017;39(2):378-403.
16. Chung CW, Mo EY, Jung GS, Kim YH, Cho SW, Park DJ, et al. Decreased Expression of Ileal Thyroid Hormone Transporters in a Hypothyroid Patient: A Case Report. Front Endocrinol (Lausanne). 2021; 12:664839.
17. Weitzman SP, Ginsburg KC, Carlson HE. Colesevelam hydrochloride and lanthanum carbonate interfere with the absorption of levothyroxine. Thyroid. 2009;19(1):77-79.
18. Zamfirescu I, Carlson HE. Absorption of levothyroxine when coadministered with various calcium formulations. Thyroid. 2011;21(5):483-486.
19. Leger CS, Ooi TC. Ferrous fumarate-induced malabsorption of thyroxine. Endocrinologist. 1999;9(6):493-495.
20. Campbell BA, Bantle JP, Schmidt BA. Sucralfate and the absorption of L-thyroxine. Ann Intern Med. 1994;121(2):152.
21. Guzman-Prado Y, Vita R, Samson O. Concomitant Use of Levothyroxine and Proton Pump Inhibitors in Patients with Primary Hypothyroidism:a Systematic Review. J Gen Intern Med. 2021;36(6):1726-1733.
22. Guzman-Prado Y, Vita R, Samson O. The impact of proton pump inhibitors on levothyroxine absorption: The good, the bad and the ugly. Eur J Intern Med.2020; 76:118-119.
23. Goldberg AS, Tirona RG, Asher LJ,Kim RB, Uum SHMV. Ciprofloxacin and rifampin have opposite effects on levothyroxine absorption. Thyroid. 2013;23(11):1374-1378.
24. Tirona RG, Leake BF, Wolkoff AW, Kim RB. Human organic anion transporting polypeptide-C (SLC21A6) is a major determinant of rifampin-mediated pregnane X receptor activation. J Pharmacol Exp Therap. 2003;304(1):223-228.
25. Aanderud S, Myking OL, Strandjord RE. The Influence of carbamazepine on thyroid-hormones and thyroxine binding globulin in hypothyroid patients substituted with thyroxine. Clin Endocrinol (Oxf). 1981;15(3):247–252.
26. Arafah BM. Decreased levothyroxine requirement in women with hypothyroidism during androgen therapy for breast cancer. Ann Intern Med. 1994;121(4):247-251.
27. Carvalho GAD, Bahls SC, Boeving A, Graf H. Effects of selective serotonin reuptake inhibitors on thyroid function in depressed patients with primary hypothyroidism or normal thyroid function. Thyroid. 2009;19(7):691-97.
28. McCowen KC, Garber JR, Spark R. Elevated serum thyrotropin in thyroxine-treated patients with hypothyroidism given sertraline. N Engl J Med. 1997;337(14):1010-1011.
29. Abdulrahman RM, Verloop H, Hoftijzer H, et al. Sorafenib-induced hypothyroidism is associated with increased type 3 deiodination. J Clin Endocrinol Metabol. 2010;95(8):3758-3762.
30. Nguyen TT, Distefano JJ, Huang M, Yamada H, Cahnmann HJ. 5'- and 5-deiodinase activities in adult rat cecum and large bowel contents inhibited by intestinal microflora. Am. J. Physiol. Metab. 1993;265: E521-24.
31. Cereijido M, Contreras RG, Flores-Benítez D, et al. new diseases derived or associated with the tight junction. Arch. Med. Res. 2007;38(5):465-78.
32. Fröhlich E, Wahl R. Microbiota and thyroid interaction in health and disease. Trends Endocrinol. Metab. 2019;30(8):479-490.
33. Spaggiari G, Brigante G, de Vincentis S,Cattini U, Roli L, Santis MCD, et al. Probiotics ingestion does not directly affect thyroid hormonal parameters in hypothyroid patients on levothyroxine treatment. Front Endocinol.2017;8:1-9.
34. Knezevic J, Starchl C, Tmava Berisha A, Amrein K. Thyroid-Gut-Axis: How Does the Microbiota Influence Thyroid Function? Nutrients. 2020;12(6):1769.
35. Bell DS, Ovalle F. Use of soy protein supplement and resultant need for increased dose of levothyroxine. Endocr Pract.2001;7(3):193-194.

36. Conrad SC, Chiu H, Silverman BL. Soy formula complicates management of congenital hypothyroidism. Arch Dis Child.2004;89(1):37-40.
37. Gatta E, Maltese V, Cavadini M,Anelli V, Bambini F, Buoso C, et al. Interference or Noninterference Between Soy and Levothyroxine: That Is the Question. A Narrative Review of Literature. Endocr Pract. 2023;29(11):897-901.
38. Chon DA, Reisman T, Weinreb JE, Hershman JM, Leung AM. Concurrent milk ingestion decreases absorption of levothyroxine. Thyroid. 2018,28(4):454-457.
39. Benvenga S, Bartolone L, Pappalardo MA, et al. Altered intestinal absorption of L -thyroxine caused by coffee. Thyroid. 2008;18(3):293-301.
40. Lai YW, Huang SM. Tea consumption affects the absorption of levothyroxine. Front Endocrinol (Lausanne). 2022; 13:943775.
41. Liel Y, Harman-Boehm I, Shany S. Evidence for a clinically important adverse effect of fiber-enriched diet on the bioavailability of levothyroxine in adult hypothyroid patients. J Clin Endocrinol Metab.1996;81(2):857-859.
42. Deiana L, Marini S, Mariotti S. Ingestionoflargeamounts of papaya fruit and impaired effectiveness of levothyroxine therapy. Endocr Pract.2012;18(1):98-100.
43. Bailey DG. Fruit juice inhibition of uptake transport: a new type of food–drug interaction. Br J Clin Pharmacol.2010;70(5):645-655.
44. Singh N, Singh PN, Hershman JM. Effect of calcium carbonate on the absorption of levothyroxine.JAMA.2000;283(21):2822-2825.
45. Singh N, Weisler SL, Hershman JM. The acute effect of calcium carbonate on the intestinal absorption of levothyroxine. Thyroid.2001;11(10):967-971.
46. Campbell NR, Hasinoff BB, Stalts H, Rao B, Wong NC. Ferrous sulfate reduces thyroxine efficacy in patients with hypothyroidism. Ann Intern Med.1992;117(12):1010-1013.
47. American Academy of Pediatrics, Rose SR, The Section on Endocrinology and Committee on Genetics, et al. Update of newborn screening and therapy for congenital hypothyroidism. Pediatrics.2006;117(6):2290-303.
48. Ant´unez PB, Licht SD. Vitamin C improves the apparent absorption of levothyroxine in a subset of patients receiving this hormone for primary hypothyroidism. Rev Argent Endocrinol Metab.2011;48(1):16-24.
49. Jubiz W, Ramirez M. Effect of vitamin C on the absorption of levothyroxine in patients with hypothyroidism and gastritis. J Clin Endocrinol Metab. 2014;99(6):E1031-4.
50. Gezer E. Morning exercise affects the absorption of oral levothyroxine: a single center pilot study. Endocrine. 2024;85(1):267-271.
51. Perez CL, Araki FS, Graf H, Carvalho GMD. Serum thyrotropin levels following levothyroxine administration at breakfast. Thyroid.2013;23(7):779-784.
52. Bach-Huynh TG, Nayak B, Loh J,Soldin S, Jonklaas J. Timing of levothyroxine administration affects serum thyrotropin concentration. JClin Endocrinol Metab.2009;94(10):3905-3912.
53. Bolk N, Visser TJ, Nijman J, Jongste TJ, Tijssen JGP, Berghout A. Effects of evening vs morning levothyroxine intake: a randomized double-blind crossover trial. Arch Intern Med .2010;170(22):1996-2003.
54. Jonklaas J, Bianco AC, Bauer AJ, Burman KD,Cappola AR, Celi FS, et al. Guidelines for the treatment of hypothyroidism: prepared by the American Thyroid Association task force on thyroid hormone replacement. Thyroid.2014;24(12):1670-751.
55. Ala S, Akha O, Kashi Z, Asgari H, Bahar A, Sasanpour N, et al. Dose administration time from before breakfast to before dinner affect thyroid hormone levels? Caspian J Intern Med. 2015 Summer;6(3):134-40.
56. Rajput R, Chatterjee S, Rajput M. Can Levothyroxine Be Taken as Evening Dose? Comparative Evaluation of Morning versus Evening Dose of Levothyroxine in Treatment of Hypothyroidism. J Thyroid Res. 2011; 2011:505239.
57. Pang X, Pu T, Xu L, Sun R. Effect of l-thyroxine administration before breakfast vs at bedtime on hypothyroidism: A meta-analysis. Clin Endocrinol (Oxf). 2020;92(5):475-481.
58. Navid A, Dayal D, Kaur H, Gupta A, Attri S. Comparative efficacy of early morning versus bedtime administration of levothyroxine in children with hypothyroidism: a prospective, open label, randomized, case-control study. Pediatr Endocrinol Diabetes Metab. 2021;27(3):178-182.
59. Akın O. Morning vs. bedtime levothyroxine administration: what is the ideal choice for children? J Pediatr Endocrinol Metab. 2018;31(11):1249-1255.
60. Mello RB, Giassi K, Stahl G, Assis MLM, Flores MS, Lima MCD, et al. Evaluation of Bedtime vs. Morning Levothyroxine Intake to Control Hypothyroidism in Older Patients: A Pragmatic Crossover Randomized Clinical Trial. Front Med (Lausanne). 2022; 9:828762.
61. Srivastava S, Sharma G, Rathore M,Chaturvedi A, Keswani P, Saxena GN, et al. A Crossover Study Evaluating Effect of Timing of Levothyroxine on Thyroid Hormone Status in Patients of Hypothyroidism. J Assoc Physicians India. 2018;66(9):37-40.
62. Radhakrishnan R, Venkatasamy S, Pyarejan KS, et al. Effectiveness of bedtime levothyroxine intake as compared to morning levothyroxine intake in children. Int J Contemp Pediatr. 2017; 4:1969-1974.
63. Moore JG, Englert E Jr. Circadian rhythm of gastric acid secretion in man. Nature. 1970;226(5252): 1261-1262.
64. Virili C, Trimboli P, Centanni M. Novel thyroxine formulations: a further step toward precision medicine. Endocrine. 2019;66(1):87-94.
65. Vandse S, Psarrakis Y, Washington K, Baron MA. Comparative Bioavailability of a Novel Solution and a Tablet Formulation of Levothyroxine. Clin Pharmacol Drug Dev. 2023;12(5):502-508.
66. Antonelli A, Elia G, Ragusa F, Paparo S, Cavallini G, Benvenga S, et al. The Stability of TSH, and Thyroid Hormones, in Patients Treated With Tablet, or Liquid Levo-Thyroxine. Front Endocrinol (Lausanne). 2021;12:633587.
67. Nagy EV, Perros P, Papini E,Katko M, Hegedüs L. New Formulations of Levothyroxine in the Treatment of Hypothyroidism: Trick or Treat? Thyroid. 2021;31(2):193-201.
68. Cappelli C, Pirola I, Daffini L,Formenti A, Iacobello C, Cristiano A, et al. A double-blind placebo-controlled trial of liquid thyroxine ingested at breakfast: results of the TICO study. Thyroid.2016;26(2): 197-202.
69. Pirola I,Gandossi E,Brancato D, Marini F, Cristiano A, Delbarba A, et al, TSH evaluation in hypothyroid patients assuming liquid levothyroxine at breakfast or 30 min before breakfast. J. Endocrinol. Investig. 2018;41(11):1301-1306.
70. Ribichini D, Fiorini G,Repaci A, Castelli V, Gatta L, Vaira D, et al.Tablet and oral liquid L-thyroxine formulation in the treatment of naïve hypothyroid patients with Helicobacter pylori infection. Endocrine.;2017;57(3):394-401.
71. Ruchała M, Bossowski A, Brzozka MM, et al. Liquid levothyroxine improves thyroid control in patients with different hypothyroidism aetiology and variable adherence - case series and review. Endokrynol Pol. 2022;73(5):893-902.
72. Fallahi P, Ferrari SM, Marchi S,Bortoli ND, Ruffilli I, Antonelli A. Patients with lactose intolerance absorb liquid levothyroxine better than tablet levothyroxine. Endocrine.2017;57(1):175-178.
73. Benvenga S,Capodicasa G, Perelli S,Ferrari SM, Fallahi P, Antonelli A.Increased requirement of replacement doses of levothyroxine caused by liver cirrhosis. Front. Endocrinol.2018; 9:150.
74. Antonelli A, Elia G, Ragusa F, Paparo SR, Cavallini G, Benvenga S, et al. The Stability of TSH, and Thyroid Hormones, in Patients Treated with Tablet, or Liquid Levo-Thyroxine. Front Endocrinol (Lausanne). 2021; 12:633587.
75. Castellana M, Castellana C, Giovanella L,Trimboli P. Prevalence of

gastrointestinal disorders having an impact on tablet levothyroxine absorption: should this formulation still be considered as the first-line therapy? Endocrine. 2020;67(2):281-290.

76. Vita R,Saraceno G, Trimarchi F, Benvenga S. Switching levothyroxine from the tablet to the oral solution formulation corrects the impaired absorption of levothyroxine induced by proton-pump inhibitors. J. Clin. Endocrinol. Metab.2014;99(12):4481-4486.
77. Benvenga S, Di Bari F,Vita R. Undertreated hypothyroidism due to calcium or iron supplementation corrected by oral liquid levothyroxine. Endocrine.2017;56(1):138-145.
78. Morini E, Catalano A,Lasco A,Morabito N, Benvenga S. In thyroxine-replaced hypothyroid postmenopausal women under simultaneous calcium supplementation, switch to oral liquid or softgel capsule L-thyroxine ensures lower serum TSH levels and favorable effects on blood pressure, total cholesterolemia and glycemia. Endocrine.
79. Gatta E, Bambini F, Buoso C,Gava M, Maltese V, Anelli V, et al. Liquid levothyroxine formulations in patients taking drugs interfering with L-T4 absorption. Front Endocrinol (Lausanne).2022;13:1080108.
80. Fallahi P, Ferrari SM, Elia G, et al. L-T4 Therapy in Enteric Malabsorptive Disorders. Front Endocrinol (Lausanne). 2021; 12:626371.
81. Peirce C, Ippolito S, Lanas A,Pesce M,Pontieri G, Arpaia D, et al. Treatment of refractory and severe hypothyroidism with sublingual levothyroxine in liquid formulation.Endocrine.2018;60(1)193-196.
82. Czernel MG, Dydejczyk AH, Kudła BK,Lewiński A, Ruchała M, Syrenicz A, et al. Expert opinion on liquid L-thyroxine usage in hypothyroid patients and new liquid thyroxine formulation - Tirosint SOL [Opiniaekspertówdotyczącasto sowani apłynnejpostacilewotyroksynyoraznowegopreparatuTirosint SOL u chorychnaniedoczynnośćtarczycy]. Endokrynol Pol. 2020;71(5):441-465.
83. Pabla D,Akhlaghi F, Zia H. A comparative pH-dissolution profile study of selected commercial levothyroxine products using inductively coupled plasma mass spectrometry. Eur J PharmBiopharm. 2009;72(1):105-110.
84. Trimboli P, Mouly S. Pharmacokinetics and Clinical Implications of Two Non-Tablet Oral Formulations of L-Thyroxine in Patients with Hypothyroidism. J Clin Med. 2022;11(12):3479.
85. Santaguida MG,Virili C, Duca SC, Cellini M, Gatto I, Brusca N, et al. Thyroxine soft gel capsule in patients with gastric-related T4 malabsorption. Endocrine. 2015;49(1):51-57.
86. S. Benvenga, Bartolone L, Squadrito S, Trimarchi F. Delayed intestinal absorption of levothyroxine. Thyroid.1995;5(4):249-253.
87. Ritter MJ, Gupta S, Hennessey JV. Alternative routes of levothyroxine administration for hypothyroidism. Curr Opin Endocrinol Diabetes Obes. 2020;27(5):318-322.
88. Opazo MC, Yañez O, Márquez-Miranda V,Santos J, Rojas M, Durán IA, et al.Increased Absorption of Thyroxine in a Murine Model of Hypothyroidism Using Water/CO2 Nanobubbles. Int J Mol Sci. 2024;25(11):5827.
89. Ducharme M, Scarsi C, Bettazzi E,Mautone G, Lewis Y, Celi FS. A Novel Levothyroxine Solution Results in Similar Bioavailability Whether Taken 30 or Just 15 Minutes Before a High-Fat High-Calorie Meal. Thyroid. 2022;32(8):897-904.