

PREFORMULATION PROBING OF LEVOTHYROXINE

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ABSTRACT

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Levothyroxine therapy is given when deficient in the thyroid hormone is found in the human body. Many circumstances physiological or quasi-physiological or clear pathologically, it can modify the absorption of levothyroxine in the human body. Levothyroxine intake may actually vary by age and patient compliance, fasting, consumption of certain foods from (fibre, grapes, soybeans, papaya, coffee, etc.) or some medicines (proton pump inhibitors, antacids, sucralfate, etc.) Cetera). In addition, there can be many gastrointestinal illnesses, including conditions and illnesses that disrupt the integrity of the intestinal barrier. Anything that affects stomach acid can alter the bioavailability of levothyroxine. Because it's the huge widespread prevalence of thyroid disease, large many patients face such problems. Therefore, forming the new levothyroxine oral preparations other than solid tablets represent an interesting therapeutic approach at the same time, simple and potent to face this problem. Recently, two different levothyroxine were introduced formulations are proposed: liquid and soft gel formulations. Such prescriptions are innovative and effective an inexpensive therapeutic approach for patients with hypothyroidism with mal-absorption problems levothyroxine.⁽⁴⁴⁾

KEYWORDS

Levo-thyroxine; Absorption; Mal-absorption; Liquid formulation;
pre-formulating

INTRODUCTION

Levothyroxine is Thyroxine (T₄), an amino acid containing iodine Derivatives embedded in glycoproteins (Thyroglobulin). This synthetic derivative is biochemically and physiologically identical Natural hormone¹. Levothyroxine therapy is used when the human body is deficient in thyroid hormone, as it occurs when there is a deficiency in the thyroid gland, pituitary gland, hypothalamus (or primary, secondary, or tertiary hypothyroidism). Levothyroxine is also used to treat normal goiter and polynodulargoiter. Including thyroid nodules, subacute or chronic for thyroiditis or postoperative^{2,4} drug absorption after deficit or radio metabolic treatment in patients with thyroid cancer is defined as transit Substances from the administration site Blood circulation (hence, this stage does not exist with intravenous administration) medicine).⁽⁴⁴⁾

PHARMACOKINETICS OF LEVOTHYROXINE IN HEALTH

The distribution of the drug is always mediated by the difference in concentration, lower at the point of application and systemic level. The absorption keeps on until there is a balance between the concentrations of drug in the blood and in the application site. The rate of absorption depends on many factors, such as the intrinsic characteristics of the drug, the pharmaceutical formulation used, and the anatomical and functional characteristics of the subject taking the medication. Whereas in most of the cases the absorption of the drug takes place through a passive process, absorption is facilitated when the drug is in the nonionized form, being more lipophilic.

After ingestion, levothyroxine is only partially absorbed in the stomach, mainly the small intestine, especially the duodenum and jejunum^{1,2}; this concept elucidates why patients bear from short bowel syndrome (following bowel resection) needed a higher dosage of levothyroxine. The ionization status of thyroxine sodium and the dissolving properties of pharmaceutical products are affected by fluctuations in intra luminal pH. With healthy volunteers fasting, sometimes Maximum concentration of levothyroxine (T_{max}) Bioavailability in about 2 hours Is 60 to 80% (these values are Eat); Volume of distribution is

about. 11.5 liters. These characteristics change in patients with hypothyroidism: T_{max} is about 3 hours, Higher bioavailability, and potentially higher distribution Capacity is about 14.7 liters^{7,10}.

The main metabolic pathway of levothyroxine is Formed by deiodination (iodine molecules are removed from carbon 5 in the outer ring Conversion to T₄) and subsequent T₃ (triiodothyronine) by deiodinase enzyme^{11,13}. If deiodination is done at the level of the T₄ inner ring, this is the product is an inactive molecule of inverted T₃. Both forms of T₃ then become T₂ (diiodotyrosine), T₁ (monoiodotyrosine), and their corresponding upside-down^{14,15}. Metabolism. The daily sales of T₄ is about 10%, It is about 50 to 70% of T₃ turnover daily T₄ is about 10%, but about 50. Equivalent to 70% of T₃ in healthy volunteers; these values are increased slightly in patients with hypothyroidism. A high proportion of T₃ and T₄ It binds to plasma proteins and has a value as 99.8 percent,^{10,16,17}. It occurs in both healthy volunteers and patients with hypothyroidism. Specifically, the percentage of T₄ that is not bound to plasma .The protein called free T₄ is 0.02-0.03%, Free T₃ does not exceed 0.2%. The protein most involved in the binding of T₃ and T₄ Thyroxine-binding globulin (TBG), Binds more than 80% of the total hormone's albumin and prealbumin^{16,18}.⁽⁴⁴⁾

CONDITIONS THAT IMPAIR THE ABSORPTION OF LEVOTHYROXINE

Many physiological or quasi-physiological or apparently pathological conditions can change the absorption of levothyroxine in the human body. Lent greatly affects the absorption of levothyroxine. Some fragments of evidence: Wenzel et al. significantly reduced absorption of levothyroxine If you take the medicine after a meal The 8th. Take Levothyroxine 15 minutes before meals do not normalize or reduce circulating TSH levels. Therefore, it is generally advisable to take levothyroxine 1 hour in advance. Bon Appetite^{19,20}. In particular, certain foods and drinks affect the absorption of levothyroxine: especially fibre, grapes, soybeans, papaya Coffee reduces drug absorption^{21,24}. Of course, patient compliance is an important factor in doing so. Correct achievement of normal thyroid levels Hormones²⁵. The age of the subject can also be adjusted Containing Levothyroxine, geriatrics with age, T₄ uptake decreased slightly, Also, catabolism to triiodothyronine, the levels of free

T3 and T3 are reduced. Many drugs can also reduce the absorption of Levothyroxine metabolism.

As mentioned earlier, there is only one stomach acid Requirement for proper intake of thyroxine. Correspondingly concepts affect the Bioavailability of PPI Therapy Drugs by reducing its absorption⁵. Reduced the use of antacids like aluminum Intestinal absorption of levothyroxine. This effect was elucidated by in vitro studies showing that small amounts of aluminum salts can adsorb levothyroxine. Its bioavailability, Proven in vivo studies concomitant use of aluminum-containing antacids in patients with hypothyroidism taking levothyroxine reduces their absorption and increases TSH levels^{26, 27}.

Relationship between sucralfate and thyroid gland the hormone is not clear yet. Many attempts have shown contradictory results. Among these, one study examined the absorption of levothyroxine in healthy volunteers with the drug 8 hours after taking sucralfate. The results showed that the time to peak absorption is altered only if the administration of the two substances is simultaneous, whereas the time to peak absorption is similar to controls if administrated after 8 hours^{28, 29}.

When the examination has been carried out in hypothyroid sufferers the consequences were different, displaying a moderate discount of serum F4 and a non significant elevation of TSH²⁹. Iron sulphate reduced the availability of thyroxine and formed an insoluble complex, as shown in in-vitro studies. Such impact results, in-vivo, in a reduced absorption of levothyroxine with the consequent boom of TSH levels³⁰.

Calcium carbonate, a phosphorus adsorbent, reduces the bioavailability of levothyroxine via way of means of adsorbing levothyroxine in an acidic environment, as proven in vivo and in vitro studies³¹. Had a similar effect observed with a phosphorus adsorbent different from Sevelamer Hydrochloride, lanthanum⁴, and other drugs cholestyramine, colesevelam, etc³². Other types of drugs reduce the bioavailability of levothyroxine and speed up metabolism and/or excretion. Rifampicin is an antibiotic that affects thyroid hormone levels and increases triiodothyronine T4 metabolism and bile excretion. Conjugated. Studies have shown that treatment with rifampicin in patients with normal thyroid function in Hashimoto's thyroiditis has clinical implications.

Hypothyroidism³³.

Many antiepileptic drugs such as phenobarbital, phenytoin, and carbamazepine increase levels of Thyroxine metabolism. This effect is due to her properties that induce liver enzymes Uridine diphosphate glucuronosyltransferase (UGT), lowering serum T4 levels³⁴. Some studies have found new biological agents its lower serum thyroxine levels like motesanib, sunitinib, imatinib, but the result is I don't know yet³⁵. Many gastrointestinal disorders also change their Levothyroxine intake. In general, it is closely related to the condition of the intestinal barrier. The intestinal barrier is It allows the absorption of nutrients, but it prevents the passage of harmful molecules It is introduced daily from the oral cavity into the gastrointestinal tract. The barrier is closely composed of many actors Related to each other: mucosal layer, epithelial components of natural and adaptive immunity, endocrine and neurointestinal systems, Vascular and lymphatic system, and digestion enzyme. Knowledge of the intestinal barrier It expanded with the establishment of the intestinal flora.

Intestinal flora known as "gut microbiota" is a new research field. The human body is completely sterile at birth; However, it comes into contact with many microbial communities at birth: In all fecal, vaginal, and skin microbiota mother. Sterile intestinal contamination causes some changes in the body. Interaction with various microorganisms Population means having children for a period of 6 to 36 months (in terms of weaning) Develop "Core Microbiota" Intestinal tract, genitourinary system, respiratory tract Systems³⁶. These core microbiota, including viruses Bacteria, and fungi accompany people in His life. The body is also in constant contact with various microbial species. It affects the fluctuation of the intestinal flora. Lifestyles play an important role place of birth, type of meal. The gut microbiota is considered the actual system with total biomass It weighs about 1 kg and is composed of many species. (Approximately 15,000).

But everyone has a pool The predominant type of bacteria (so-called enterotype). Various enterotypes metabolize foods like complex carbohydrates and other substances. An episode of this phenomenon is the effect of various enterotypes on the pharmacokinetics of drugs. Colon Microbiota and intestinal barrier engage others to alter the consumption of all ingested substances, along with drugs, and consequently levothyroxine. Some conditions can affect the intestines barrier. The theory of "dysbiosis" is as follows. Based on changes in the composition

of Gut microbiota with increased toxic substances reduced type and protection This causes inflammation of the intestines (for example, during treatment with illness or antibiotics or proton pump inhibitors).

Because the inner wall of the intestine is constantly damaged, enterocytes are actually separated by tight junctions and desmosomes. Maintains the correct magnetic permeability and is covered through a layer of mucus produced by the cup Cells that are expressed differently in different areas of the gastrointestinal tract. For example, the mucosal layer is thicker in the large intestine and thinner in the small intestine. The mucus layer is composed of an inner layer (inner layer) and an outer layer (outer layer) in which bacteria that make up the intestinal flora are present live ³ under certain conditions similar to gastroenteritis, the mucosal layer is damaged and mutualistic bacteria directly enterocytes that lead to epithelial damage and immune activation. There is also one in the intestinal angiogenesis Important role: In ischemic conditions (atherosclerosis or vasoconstriction) enterocytes cause increased intestinal permeability, resulting in the passage of fragments of bacteria in the lamina propria. Many gastrointestinal disorders, such as diseases that disrupt the integrity of the intestinal barrier and affect stomach acid Levothyroxine. Celiac disease that correlates with hypothyroidism for two reasons: there is a link even with autoimmune thyroiditis and celiac disease Patients with elevated TSH, their levels eating a gluten-free diet normalizes hormones, but altering the intestinal barrier is so important that levothyroxine doses should be reduced. With celiac disease, These pathophysiological phenomena, less frequently, have been reported in patients with inflammatory bowel disease. Obvious anatomical changes in the intestine as a result of excision of the small intestine Obesity surgery, inclusion Levothyroxine. Both lactose intolerance syndrome and small intestinal bacterial overgrowth (SIBO) ^{37,38} are associated with low serum levels. Thyroxine levels, but SIBO did not affect T3 and hormone levels T4. Finally, Helicobacter pylori can die Using the bioavailability of levothyroxine in two ways Increased gastric pH. H. pylori produces neutralized stomach acid, for reduced chronic atrophic gastritis Gastric acid secretion ^{5,39, (44)}

NEW THERAPEUTIC STRATEGIES FOR PATIENTS WITH IMPAIRED ABSORPTION OF LEVOTHYROXINE

Since then, the tremendous prevalence of thyroid disease that many patients have to deal with such a problem. In addition, repeating serum thyroid hormone doses to adjust the therapeutic dose can make it a serious economic dose load ⁴⁰. Since the dissolution of solid tablets is an essential step to cross the intestinal barrier, their absorption is ^{21,41} compared to liquid. Recently, two different levothyroxine's were introduced Formulations are proposed: liquid and soft gel formulations. The liquid oral preparation of levothyroxine (Made by IBSA InstitutBiochimique SA, Lugano, Switzerland) is available. It has Proven in both in vitro studies and animal experiments in the investigation, Tablet. It was also used in human pediatric studies These preliminary results were confirmed by volunteers ⁴¹. Liquid levothyroxine does not need to be How the tablet dissolves Like the two preliminary ones, it is less dependent on gastric pH and malabsorption status study ^{40,42}. Bernareggi, et al ²⁵ certainly shows Its diet, especially breakfast, reduces the bioavailability of liquid levothyroxine. human body.

This feature patient needs to take medicine 60 A few minutes before breakfast (actually this limit is may affect treatment compliance). In the case series by Pirola et al. ⁴² however, there are liquid formulations of levothyroxine population. Now at normal TSH level patients with hypothyroidism have previously had gastric bypass surgery with Rouxen Y the person who developed the postoperative increase serum TSH levels despite taking levothyroxine tablets. There is also liquid absorption Levothyroxine is not affected as in the case of solid formulation from coffee consumption. Recent studies compared TSH, FT3, and FT4 Concentrations of patients taking liquid levothyroxine Breakfast with 3 and coffee received the same management after 6 months dosage, 30 minutes before breakfast patient enrolled in the study had normal thyroid function absorption disorder.

There was no difference in Thyroid hormone levels at 3- and 6-months administration of levothyroxine took 30 minutes please respect TSH, FT3, FT4 before breakfast. Oral, therefore, liquid levothyroxine can die It is difficult to solve the problems of these patients' postponing coffee for 1 hour ⁴³ with LT4 therapy. Soft capsule or soft gel formulation Innovative form of levothyroxine .It is designed to overcome the problems associated with malabsorption conditions. Softgel capsules are

designed to turn liquid formulations into solids in the form of medicine. Therefore, they are a practical combination of solid products (especially vulnerable population group) like this old patient experiencing frequent dysfunction of the esophagus, especially paradoxical dysphagia) and qualities (Like the lack of need for resolution Phase), which makes liquid formulations more effective than tablets in terms of pharmacokinetics, absorption, and bioavailability²¹.

Soft gel capsules consist of a liquid or semi-solid matrix surrounded by an outer gelatinous shell. This wording also applies to Levothyroxine has interesting results. As reported by Yue et al. It is shown 40, Levothyroxine in the form of soft gel capsules is absorbed faster Tablet formulation. Also, comparing soft capsule formulation goes well with tablets the dependence on changes in intra luminal pH was negligible. In addition, with food Coffee consumption doesn't seem to have any effect Bioavailability of levothyroxine when ingested in the form of soft gel^{21, (44)}

CONCLUSION

The use of various pharmaceutical formulations represents an innovative, powerful, and reasonably-priced healing technique to the hypothyroid sufferers with troubles of impaired absorption of levothyroxine.

REFERENCES

1) HAYS MT. Localization of human thyroxine absorption. *Thyroid* 1991; 1: 241-248.

2) HAYS MT. Thyroid hormone and the gut. *Endocrine Res* 1988; 14: 203-224.

3) LIWANPO L, HERSHMAN JM. Conditions and drugs interfering with thyroxine absorption. *Best Pract Res Clin Endocrinol Metab* 2009; 23: 781-792.

4) JOHN-KALARICKAL J, PEARLMAN G, CARLSON HE. New medications which decrease levothyroxine absorption. *Thyroid* 2007; 17: 763-765.

5) CENTANNI M, GARGANO L, CANETTIERI G, VICECONTI N, FRANCHI A, DELLE FAVE G,

ANNIBALE B. Thyroxine in goiter, *Helicobacter pylori* infection, and chronic gastritis. *N Engl J Med* 2006; 354: 1787-1795.

6) SACHMECHI I, REICH DM, ANINYEI M, WIBOWO F, GUPTA G, KIM PJ. Effect of proton pump inhibitors on serum thyroid-stimulating hormone level in euthyroid patients treated with levothyroxine for hypothyroidism. *Endocrine Pract* 2007; 13: 345-349.

7) BENVENGA S, BARTOLONE L, SQUADRITO S, LO GIUDICE F, TRIMARCHI F. Delayed intestinal absorption of levothyroxine. *Thyroid* 1995; 5: 249-253.

8) WENZEL KW, KIRSCHSIEPER HE. Aspects of the absorption of oral L-thyroxine in normal man. *Metabolism* 1977; 26: 1-8.

9) READ DG, HAYS MT, HERSHMAN JM. Absorption of oral thyroxine in hypothyroid and normal man. *J Clin Endocrinol Metab* 1970; 30: 798-799.

10) NICOLOFF JT, LOW JC, DUSSAULT JH, FISHER DA. Simultaneous measurement of thyroxine and triiodothyronine peripheral turnover kinetics in man. *J Clin Invest* 1972; 51: 473-483.

11) MOL JA, VISSER TJ. Rapid and selective inner ring deiodination of thyroxine sulfate by rat liver deiodinase. *Endocrinology* 1985; 117: 8-12.

12) BALSAM A, SEXTON F, BORGES M, INGBAR SH. Formation of diiodotyrosine from thyroxine. Ether-link cleavage, an alternate pathway of thyroxine metabolism. *J Clin Invest* 1983; 72: 1234-1245.

13) PITTMAN CS, CHAMBERS JB JR, READ VH. The extrathyroidal conversion rate of thyroxine to triiodothyronine in normal man. *J Clin Invest* 1971; 50: 1187-1196.

14) ROBBINS J. Factors altering thyroid hormone metabolism. *Environ Health Perspect* 1981; 38: 65-70.

15) ENGLER D, MERKELBACH U, STEIGER G, BURGER AG. The mono deiodination of tri iodo thyronine and reverse

- triiodothyronine in man: a quantitative evaluation of the pathway by the use of turnover rate techniques. *J Clin Endocrinol Metab* 1984; 58: 49- 61.
- 16) UTIGER RD. Serum triiodothyronine in man. *Annu Rev Med* 1974; 25: 289-302.
- 17) BRAVERMAN LE, VAGENAKIS A, DOWNS P, FOSTER AE, STERLING K, INGBAR SH. Effects of replacement doses of sodium L-thyroxine on the peripheral metabolism of thyroxine and triiodothyronine in man. *J Clin Invest* 1973; 52: 1010-1017.
- 18) BENVENGA S, GREGG RE, ROBBINS J. Binding of thyroid hormones to human plasma lipoproteins. *J Clin Endocrinol Metab* 1988; 67: 6-16.
- 19) BACH-HUYNH TG, NAYAK B, LOH J, SOLDIN S, JONKLAAS J. Timing of levothyroxine administration affects serum thyrotropin concentration. *J Clin Endocrinol Metab* 2009; 94: 3905-3912.
- 20) BOLK N, VISSER TJ, NIJMAN J, JONGSTE IJ, TIJSEN JG, BERGHOUT A. Effects of evening vs morning levothyroxine intake: a randomized double-blind crossover trial. *Arch Intern Med* 2010; 170: 1996- 2003.
- 21) VITA R, SARACENO G, TRIMARCHI F, BENVENGA S. A novel formulation of L-thyroxine (L-T4) reduces the problem of L-T4 malabsorption by coffee observed with traditional tablet formulations. *Endocrine* 2013; 43: 154-160.
- 22) CHIU AC, SHERMAN SI. Effects of pharmacological fiber supplements on levothyroxine absorption. *Thyroid* 1998; 8: 667-671.
- 23) DEIANA L, MARINI S, MARIOTTI S. Ingestion of large amounts of papaya fruit and impaired effectiveness of levothyroxine therapy. *EndocrPract* 2012; 18: 98-100.
- 24) LILJA JJ, LAITINEN K, NEUVONEN PJ. Effects of grapefruit juice on the absorption of levothyroxine. *Br J Clin Pharmacol* 2005; 60: 337-341.
- 25) BERNAREGGI A, GRATA E, PINORINI MT, CONTI A. Oral liquid formulation of levothyroxine is stable in breakfast beverages and may improve thyroid patient compliance. *Pharmaceutics* 2013; 5: 621- 633.
- 26) LIEL Y, SPERBER AD, SHANY S. Nonspecific intestinal adsorption of levothyroxine by aluminum hydroxide. *Am J Med* 1994; 97: 363-365.
- 27) SPERBER AD, LIEL Y. Evidence for interference with the intestinal absorption of levothyroxine sodium by aluminum hydroxide. *Arch Intern Med* 1992; 152: 183-184.
- 28) SHERMAN SI, TIELENS ET, LADENSON PW. Sucralfate causes malabsorption of L-thyroxine. *Am J Med* 1994; 96: 531-535.
- 29) CAMPBELL JA, SCHMIDT BA, BANTLE JP. Sucralfate and the absorption of L-thyroxine. *Ann Intern Med* 1994; 121: 152.
- 30) CAMPBELL NR, HASINOFF BB, STALTS H, RAO B, WONG NC. Ferrous sulfate reduces thyroxine efficacy in patients with hypothyroidism. *Ann Intern Med* 1992; 117: 1010-1013.
- 31) SINGH N, SINGH PN, HERSHMAN JM. Effect of calcium carbonate on the absorption of levothyroxine. *JAMA* 2000; 283: 2822-2825.
- 32) WEITZMAN SP, GINSBURG KC, CARLSON HE. Colesevelam hydrochloride and lanthanum carbonate interfere with the absorption of levothyroxine. *Thyroid* 2009; 19: 77-79.
- 33) TAKASU N, TAKARA M, KOMIYA I. Rifampin-induced hypothyroidism in patients with Hashimoto's thyroiditis. *N Engl J Med* 2005; 352: 518-519.
- 34) BENEDETTI MS, WHOMSLEY R, BALTES E, TONNER F. Alteration of thyroid hormone homeostasis by antiepileptic drugs in humans: involvement of glucuronosyltransferase induction. *Eur J Clin Pharmacol* 2005; 61: 863-872.

35) SHERMAN SI, WIRTH LJ, DROZ JP, HOFMANN M, BASTHOLT L, MARTINS RG, LICITRA L, ESCHENBERG MJ, SUN YN, JUAN T, STEPAN DE, SCHLUMBERGER MJ. Motesanib di-phosphate in progressive differentiated thyroid cancer. *N Engl J Med* 2008; 359: 31-42.

36) DE FILIPPO C, CAVALIERI D, DI PAOLA M, RAMAZZOTTI M, POULLET JB, MASSART S, COLLINI S, PIERACCINI G, LIONETTI P. Impact of diet in shaping gut micro biota revealed by a comparative study in children from Europe and rural Africa. *Proc Natl Acad Sci U S A* 2010; 107: 14691-14696.

37) LAURITANO EC, BILOTTA AL, GABRIELLI M, SCARPELLINI E, LUPASCU A, LAGINESTRA A, NOVI M, SOTTILI S, SERRICCHIO M, CAMMAROTA G, GASBARRINI G, PONTECORVI A, GASBARRINI A. Association between hypothyroidism and small intestinal bacterial overgrowth. *J Clin Endocrinol Metab* 2007; 92: 4180-4184.

38) LIN HC. Small intestinal bacterial overgrowth: a framework for understanding irritable bowel syndrome. *JAMA* 2004; 292: 852-858.

39) VITA R, BENVENGA S. Tablet Levo thyroxine (L-T4) mal absorption induced by proton pump inhibitor: a problem that was solved by switching to L-T4 in soft gel capsule. *Endo cr Pract* 2013 Nov 18: 1-11.

40) YUE CS, SCARSI C, DUCHARME MP. Pharmacokinetics and potential advantages of a new oral solution of levothyroxine vs. other available dosage forms. *Arzneimittelforschung* 2012; 62: 631-636.

41) CASSIO A, MONTI S, RIZZELLO A, BETTOCCHI I, BARONIO F, D'ADDABBO G, BAL MO, BALSAMO A. Comparison between liquid and tablet formulations of levothyroxine in the initial treatment of congenital hypothyroidism. *J Pediatr* 2013; 162: 1264-1269, 1269.e1-2.

42) PIROLA I, FORMENTI AM, GANDOSSI E,

MITTEMPERGHER F, CASELLA C, AGOSTI B, CAPPELLI C.

Oral liquid L-thyroxine (L-t4) may be better absorbed compared to LT4 tablets following bariatric surgery. *Obesity Surg* 2013; 23: 1493-1496.

43) CAPPELLI C, PIROLA I, GANDOSSI E, FORMENTI A, CASTELLANO M. Oral liquid levothyroxine treatment at breakfast: a mistake? *Eur J Endocrinol* 2013; 170: 95-99.

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