

Levothyroxine absorption in health and disease, and new therapeutic perspectives

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Abstract. – Levothyroxine therapy is used in case of deficiency of the thyroid hormones in the human organism. Many conditions, either physiological or parapsychological or clearly pathological, can alter the levothyroxine absorption in the human body. Levothyroxine absorption can indeed be impaired by age, patient's compliance, fasting, the intake of certain foods (such as dietary fibers, grapes, soybeans, papaya and coffee) or by some drugs (such as proton-pump inhibitors, antacids, sucralfate, et cetera). Additionally, many gastrointestinal diseases, such as the conditions that disrupt the integrity of the intestinal barrier and the diseases that impair gastric acidity, may alter the bioavailability of levothyroxine. Since the enormous, widespread diffusion of thyroid diseases, a large number of patients have to face such issues. Therefore, the development of new levothyroxine oral formulations, other than solid tablets, may represent an interesting therapeutic approach, at the same time simple and effective, to face this problem. Recently, two different levothyroxine formulations have been proposed: the liquid formulation and the *softgel* formulation. Such formulations represent an innovative, effective and cheap therapeutic approach to hypothyroid patient with problems of impaired absorption of levothyroxine.

Key Words:

Levothyroxine, Absorption, Malabsorption, Liquid formulation, Gut barrier, Gut microbiota.

Introduction

Levothyroxine is the levorotatory isomer of thyroxine (T₄), a iodine-containing aminoacidic derivative which is embedded in a glycoprotein (thyroglobulin). This synthetic derivative is biochemically and physiologically identical from the natural hormone¹.

Levothyroxine therapy is used in case of deficiency of the thyroid hormones in the human organism, as it happens under deficiency of thyroid, pituitary and hypothalamic glands (respec-

tively primary, secondary and tertiary hypothyroidism). Levothyroxine is also used in the treatment of euthyroid goiter and multinodular goiter, including thyroid nodules, subacute or chronic thyroiditis, or in the case of a post-surgical deficit, or after radiometabolic treatment in patients with thyroid cancer²⁻⁴.

Pharmacokinetics of Levothyroxine in Health

The drug absorption is defined as the passage of the substance from the administration site to the bloodstream (therefore, this phase is not present in the case of intravenous administration of the drug). The drug distribution is always mediated by a concentration difference, higher at the application site and lower at the 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 the non-ionized form, being more lipophilic.

Once ingested, levothyroxine is assimilated only for a little fraction in the stomach, being mainly absorbed in the small intestine, in particular in duodenum and jejunum^{1,2}; this concept explains why patients suffering from short bowel syndrome (following bowel resection) require a higher dosage of levothyroxine. The gastric pH is another factor that influences the absorption of levothyroxine, in an inversely proportional manner (the absorption capacity decreases with the increase of gastric pH)^{5,6}: the ionization state of thyroxine sodium and the dissolution properties of the pharmaceutical preparation are affected by the variations of the intraluminal pH.

In healthy volunteers under fasting, the time of maximum concentration (T_{max}) of levothyroxine is approximately 2 hours and the bioavailability is 60-80% (these values are delayed by the meal); the distribution volume is approximately 11.5 liters. These properties change for hypothyroid patients: the T_{max} is about 3 hours, the bioavailability may be higher and the distribution volume is about 14.7 liters⁷⁻¹⁰.

The main metabolic pathway of levothyroxine is constituted by deiodination (with removal of a iodine molecule from the carbon 5 of the outer ring of T₄ by deiodinase enzyme) and consequent transformation to T₃ (triiodothyronine)¹¹⁻¹³. If the deiodination occurs at the level of the T₄ inner ring, the product is a molecule of reverse T₃, which is inactive. Both forms of T₃ are subsequently metabolized to T₂ (diiodotyrosine), T₁ (monoiodotyrosine), and their corresponding inverted^{14,15}. The daily turnover of T₄ is approximately 10%, while that of T₃ is approximately 50-70%. The turnover rate for daily T₄ is about 10% while it is around 50-70% of T₃ in healthy volunteers; these values are slightly increased in hypothyroid patients.

A high percentage of both T₃ and T₄ are bound to plasma proteins, with a value greater than 99.8%^{10,16,17}; it happens both in healthy subjects and in patients with hypothyroidism. In particular, the T₄ percentage not bound to plasma proteins, named free T₄, is the 0.02 to 0.03%, while the free T₃ does not exceed 0.2%. The proteins most involved in the binding of T₃ and T₄ are the thyroxine-binding globulin (TBG), which binds more than 80% of the total hormones, albumin and prealbumin^{16,18}.

Conditions that Impair the Absorption of Levothyroxine

Many conditions, either physiological or parapsychological or clearly pathological, can alter the levothyroxine absorption in the human body.

The fasting period strongly influences the absorption of levothyroxine, as demonstrated by several evidences: as shown by Wenzel et al, the absorption of levothyroxine is greatly diminished if the drug is taken after a meal⁸. Even taking levothyroxine 15 minutes before the meal, circulating TSH values do not normalize or reduce. Therefore, the common recommendation is to ingest levothyroxine about an hour before a meal^{19,20}. In particular, certain foods and drinks affect the absorption of levothyroxine: in particular, dietary fibers, grapes, soybeans, papaya and coffee reduce the absorption of the drug²¹⁻²⁴. Pa-

tient compliance is, of course, a key factor for the proper achievement of normal levels of thyroid hormones²⁵. The subject's age also can modulate the absorption of levothyroxine: in the geriatric age, the absorption of T₄ is slightly reduced, and also its catabolism to triiodothyronine, so that the levels of free T₃ and T₃ are decreased.

Many drugs can affect both the absorption and metabolism of levothyroxine.

As already discussed, the gastric acidity is an essential requirement to obtain the adequate absorption of thyroxine. In agreement with this concept, PPI therapy affects the bioavailability of the drug by decreasing its absorption⁵.

The use of antacids such as aluminium reduces the intestinal absorption of levothyroxine. This effect has been elucidated through *in vitro* studies, which showed that a small dose of aluminium salt is able to adsorb levothyroxine, reducing its bioavailability. *In vivo* studies demonstrated that the concurrent treatment with aluminium containing antacids in hypothyroid patients assuming levothyroxine, reduces its absorption, resulting in increased TSH levels^{26,27}.

The relation between sucralfate and thyroid hormones is still not clarified. Many trials show conflicting results. Among these, a study has evaluated the absorption of levothyroxine in healthy volunteers undertaking the drug concurrently and 8 hours after the assumption of 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 study has been conducted in hypothyroid patients the results have been different, showing a slight reduction of serum F₄ and a non-significant elevation of TSH²⁹.

The ferrous sulphate reduced the availability of thyroxine, forming an insoluble complex as shown *in vitro* studies. Such effect results, *in vivo*, in a decreased absorption of levothyroxine with consequent increase of TSH levels³⁰.

The phosphate binder calcium carbonate reduces the bioavailability of levothyroxine adsorbing it in an acid environment, as shown *in vivo* and *in vitro* studies³¹. A similar effect has been observed in other phosphate binder as sevelamer hydrochloride, lanthanum⁴ and in other drugs such as cholestyramine and colesteslam³².

Other types of drugs, reduces the bioavailability of levothyroxine accelerating the metabolism and/or excretion.

Rifampicin is an antibiotic that affects the thyroid hormones levels increasing the T4 metabolism and the biliary excretion of iodothyronine conjugates. Studies have shown that the treatment with rifampicin in euthyroid patients affected by Hashimoto's thyroiditis results in a clinical hypothyroidism³³.

Many antiepileptic drugs, such as phenobarbital, phenytoin and carbamazepine increase the thyroxine metabolism. This effect, due to their property of inducing the hepatic enzyme uridinediphosphateglucuronosyltransferase (UGT), results in a lower T4 serum levels³⁴.

Some studies showed that new biologic agents such as Motesanib, Sunitinib and Imatinib decrease the thyroxine serum levels, but results are still uncertain³⁵.

Also many gastrointestinal diseases alter the absorption of levothyroxine. In general, it is closely tied to the state of the intestinal barrier. The intestinal barrier is a functional unit that, while allowing the absorption of nutrients, prevents the passage of harmful molecules that are daily introduced by the oral cavity in the digestive tract.

The barrier consists of a set of actors closely related each other: the mucosal layer, the epithelial components of natural and acquired immunity, the endocrine and the neuroenteric system, the vascular and lymphatic system and the digestive enzymes. The knowledge of the intestinal barrier has expanded with the establishment of the intestinal microbiota. The intestinal flora, known as "gut microbiota" is an evolving field of research. The human body is completely sterile at birth, but already at the time of birth comes into contact with a number of microbial communities: among all the fecal, vagina and skin microbiota of the mother.

The contamination of a germ-free intestine causes several changes in the body.

The interaction with the different microbial populations means that child, in a period between 6 and 36 months (in relation to weaning), develop a "core microbiota" that colonizes the intestinal tract, genito-urinary and respiratory systems³⁶.

This core microbiota, which includes viruses, bacteria and fungi, will accompany the human being throughout life. The body is also in constant contact with various microbial species that influence the variability of the gut microbiota.

An important role have the habits of life, the place of birth, the type of diet. Gut microbiota is

considered a real system having a total biomass of about 1 kg, and consist of numerous species (about 15,000). Everyone, however, has a pool of dominant bacterial species (the so-called enterotype).

Different enterotype may have many ability to metabolize foods, such as complex carbohydrates, and other substances. One consequence of this phenomenon is the influence of different enterotype on the pharmacokinetics of drugs. Gut microbiota and intestinal barrier interact each other in the regulation of the absorption of all ingested substances, including drugs, and, therefore, levothyroxine.

Several conditions can impair the intestinal barrier. The theory of "intestinal dysbiosis" is based on the alteration of the composition of the gut microbiota with an increase of harmful species and a decrease of the protective ones (such as during illness or treatment with antibiotics or proton pump inhibitors), resulting in intestinal inflammation.

Since the intestinal mucosa is exposed to continuous damages, the enterocytes in fact, are separated by tight junctions and desmosomes, which maintain a correct permeability and are covered by a layer of mucus, produced by the goblet cells, which is differently expressed in the various areas of the gastrointestinal tract. For example, the mucosal layer is thicker in the large bowel and thinner in the small intestine.

The mucus layer is composed of an inner portion (inner layer), and an outer portion (outer layer), where the bacteria composing gut microbiota reside.

In some conditions³, such as during gastroenteritis, the layer of mucus is damaged and mutualistic bacteria are directly connected with the enterocytes, causing epithelial damage and immune activation.

Also the vascularization of the intestine has an important role: in ischemic conditions (atherosclerosis or vasoconstriction) the damage of the enterocytes causes an increase in intestinal permeability and consequent passage of fragments of bacterial in the lamina propria.

Many gastrointestinal diseases, for example, the conditions that disrupt the integrity of the intestinal barrier and the diseases that impair gastric acidity, may alter the bioavailability of levothyroxine.

Celiac disease that is correlated with hypothyroidism for two reasons: there is an association with autoimmune thyroiditis, and, also, in celiac

patients with elevation of TSH, the levels of this hormone normalize after gluten-free diet, requiring lower doses of levothyroxine, due to the importance of the alteration of the intestinal barrier in celiac disease. These pathophysiological phenomena have been reported, albeit less frequently, in patients with inflammatory bowel disease.

Obviously, intestinal anatomical changes, consequent to the resection of the small intestine or bariatric surgery, may affect the absorption of levothyroxine. Both lactose intolerance syndrome that bacterial overgrowth of the small intestine (SIBO, small intestinal bacterial overgrowth)^{37,38} have been associated with low serum levels of thyroxine, although the eradication of SIBO did not influence hormone levels of T3 and T4. Finally, *Helicobacter pylori* may reduce the bioavailability of levothyroxine in two ways with the increase in gastric pH. *H. pylori* produces urease which neutralizes stomach acid and can bring to chronic atrophic gastritis with decreased gastric acid secretion^{5,39}.

New Therapeutic Strategies for Patients with Impaired Absorption of Levothyroxine: the Role of Different Drug Formulations

Several factors, such as age, patient compliance, drugs, and many digestive diseases can affect the absorption of levothyroxine. Since the enormous, widespread diffusion of thyroid diseases, a large number of patients have to face such issues. Additionally, the repetition of thyroid hormone serum dosages to adjust therapeutic posology can result in a heavy economical burden⁴⁰.

Since the dissolution of solid tablets is a mandatory step for their passage through the intestinal barrier, their absorption is delayed in comparison to liquids^{21,41}.

Therefore, the development of new levothyroxine oral formulations, other than solid tablets, may represent an interesting therapeutic approach, at the same time simple and effective, to face this problem. Recently, two different levothyroxine formulations have been proposed: the liquid formulation and the *softgel* formulation.

A liquid oral formulation of levothyroxine (manufactured by IBSA Institut Biochimique SA, Lugano, Switzerland) is available. It has been shown, in both *in vitro* studies and animal studies, a higher bioavailability compared to the tablets. In addition, in a study of human pediatric subjects, these preliminary results have been con-

firmed⁴¹. Liquid levothyroxine does not need to be dissolved as tablets do, therefore it might be less dependent on the gastric pH and malabsorption conditions, as shown by two preliminary studies^{40,42}. Bernareggi et al²⁵ have indeed shown that meals, in particular breakfast, does not influence the bioavailability of liquid levothyroxine in the human body. This feature would eliminate the need for the patient to take the medication 60 minutes before breakfast (in fact, this constraint may adversely affect compliance with therapy). In a case series reported by Pirola et al⁴², however, the liquid formulation of levothyroxine has brought to normal TSH values a population of hypothyroid patients previously undergone to gastric bypass surgery according to Roux-en-Y who had developed a postoperative increase in serum TSH levels despite taking levothyroxine tablets. Moreover, the absorption of liquid levothyroxine is not affected, as it is the case for the solid formulation, by the consumption of coffee. A recent study compared TSH, FT3 and FT4 levels of patients taking liquid levothyroxine at breakfast with coffee, with those obtained 3 and 6 months later the administration of same dosage, 30 minutes before breakfast. The patients enrolled in the study were euthyroid and with no impaired absorption. There was no difference in thyroid hormone levels after 3 and 6 months of levothyroxine administration taken thirty minutes before breakfast respect TSH, FT3 and FT4. Oral liquid levothyroxine may, therefore, remove the problem of those patients find difficult to comply with LT4 therapy of postponing coffee by 1h⁴³.

The soft capsule or softgel formulation is an innovative form of levothyroxine, which has been designed to overcome issues related to malabsorption conditions. The term "softgel" is a portmanteau of "soft jellies". Softgel capsules are designed to convert the liquid formulation in solid form of a drug. They, therefore, represent the combination of the practicality of the solid formulation (in particular in fragile populations such as that geriatric patients, who experience frequently functional disorders of the esophagus, especially paradoxical dysphagia) and qualities (such as the absence of need of the dissolution phase) that make the liquid formulation more effective than tablets with regard to pharmacokinetics, absorption and bioavailability²¹. The softgel capsule consists of a liquid or semisolid matrix enclosed within an outer gelatinous shell. This formulation has also been applied to levothyroxine, with interesting results. As shown

by Yue et al⁴⁰, the absorption of levothyroxine administered as softgel capsules is more rapid than tablet formulation. Furthermore, in comparison to the tablets, the soft capsule formulation has shown a negligible dependence by changes in intraluminal pH. Moreover, both the meal and the consumption of coffee does not seem to affect the bioavailability of levothyroxine when taken in the form of softgels²¹.

Conclusions

The use of different pharmaceutical formulations represents an innovative, effective and cheap therapeutic approach to hypothyroid patient with problems of impaired absorption of levothyroxine.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

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