Gastrointestinal Malabsorption of Thyroxine

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ABSTRACT Levothyroxine, a largely prescribed drug with a narrow therapeutic index, is often a lifelong treatment. The therapeutic efficacy of T4 may be marred by behavioral, pharmacologic, and pathologic issues acting as interfering factors. Despite a continuous search for an optimal T4 treatment, a significant number of patients fail to show a complete chemical and/or clinical response to this reference dose of T4. Gastrointestinal malabsorption of oral T4 represents an emerging cause of refractory hypothyroidism and may be more frequent than previously reputed. In this review, we examine the pharmacologic features of T4 preparations and their linkage with the intestinal absorption of the hormone. We have stressed the major biochemical and pharmacologic characteristics of T4 and its interaction with the putative transporter at the intestinal level. We have examined the interfering role of nutrients, foods, and drugs on T4 absorption at the gastric and intestinal levels. The impact of gastrointestinal disorders on T4 treatment efficacy has been also analyzed, in keeping with the site of action and the interfering mechanisms. Based on the evidence obtained from the literature, we also propose a schematic diagnostic workup for the most frequent and often hidden gastrointestinal diseases impairing T4 absorption. ***(Endocrine Reviews 40: 118 – 136, 2019)***

The efficacy of a drug depends on several factors, including the appropriate dose, mode of ingestion, absorption, and potential interfering factors (1–4). This is particularly true for drugs with a narrow therapeutic index, which means significant variations of effectiveness for small variations of dose (5). T4 is one such drug with its treatment having been significantly changed over the years, based on the availability of more sensitive indexes of efficacy (2). The availability of more sensitive TSH assays, in fact, led to a progressive general reduction of T4 dose for both replacement and TSH suppressive purposes (2). A significant reduction of the harmful effects of both undertreatment and overtreatment has been observed over the years (1, 3, 6), with particular emphasis on T4 treatment during gestation (7), at doses that are adequate for both the fetus and successful progression of pregnancy. The continuous search for an optimal daily T4 replacement has led to the 1.6 to 1.8 μg/kg body weight/d consensus dose, a posology that is able to restore TSH into the normal range in most patients with hypothyroidism (4). However, a number of interfering issues often render a dose inadequate for one patient that is satisfactory for another (8). It has been reported that 20% to 50% of patients fail to show a complete chemical and/or clinical response to a reference dose of T4 (9). The consequence of this is the need for an increased dose, care, and monitoring (10). The resulting repetition of unnecessary diagnostic workup represents a substantial hidden cost for the national health systems. So far, several psychological,

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ESSENTIAL POINTS

- Gastrointestinal malabsorption of T4 may account for a significant fraction of refractory hypothyroidism
- pH is a major determinant of T4 fate in multiple metabolic steps and even in the absorption of oral T4
- The most frequent conditions that must be taken into account are *Helicobacter pylori* infection, lactose maldigestion, and celiac disease
- Unawareness of T4 malabsorption cause may lead to repeated adjustments of dose and monitoring
- The individualization of treatment helps in detecting gastrointestinal malabsorption of T4
- The schematic diagnostic workup to detect gastrointestinal disorders should start based on the clinical features and the prevalence of gastrointestinal disorders
- T4 treatment may be used as a tool to reveal occult gastrointestinal diseases

nutritional, and pharmacological events may be responsible for the increased requirement for T4 in these patients (for reviews, see Refs. 2–4 and 11–13), with some of these events deserving mention. Because of poor compliance with the prescribed regimen, certain patients do not take T4 regularly, a condition known as pseudomalabsorption (14) and once reputed to account for most of the increased requirement of T4. T4 dose has to be sometimes increased when different T4 preparations are available and a patient switches one to another (for a review, see Ref. 2). Once pseudomalabsorption has been excluded, impaired intestinal absorption of T4 caused by nutrients, drugs, and gastrointestinal disorders represents a major cause of refractory hypothyroidism. In the era of precision medicine (15), treatment should be highly individualized and all the characteristics of a drug should be taken into account during a chronic and sometimes lifelong treatment.

In this review, we examine the pharmacologic features of T4 preparations and their linkage with the clinical evidence of a reduced intestinal absorption of the hormone.

How the Pharmaceutical Forms of Oral T4 Are Prepared

Typically, leaflets on medicines and websites of drug companies fail to give technical information on manufacturing of their products, and T4 is no exception. In general, tablets, which are most often disc-shaped, are a solid dispersion of the active ingredient and disintegrable excipients, pressed or compacted from a powder into a solid dose. Excipients have several functions, and the same excipient may serve more than one function (Table 1) (16). Examples of such functions are to improve powder flowability (gliding), to favor cohesion of different substances (binding), to facilitate tablet disintegration in the gastrointestinal tract, or to prevent the tablet from sticking (lubrication) (17). To ease swallowing and to resist environmental conditions, the tablet is coated with a polymer. Examples of glidants are magnesium stearate and talc; examples of binders are lactose, starch, cellulose, and polyvinylpyrrolidone; examples of disintegrants are polyvinylpyrrolidone and sodium carboxymethyl cellulose (croscarmellose sodium); and examples of lubricants are talc, silica, and magnesium stearate (16, 17). Clearly, these ingredients must be granulated prior to compression to assure even distribution of the active ingredient and to contain the appropriate amount of active ingredient in each tablet (17). In one report (18), some intolerance to the excipients used to prepare tablet T4 has been observed. Recently, refractory hypothyroidism linked to improper storage of T4 tablets has also been shown. This suggests that in addition to proper mode of ingestion, patients should be instructed on proper modalities of T4 storage (19).

As summarized elsewhere (20), softgel capsules are composed of an outer gelatin shell and by a fill formulation, and the highly specialized manufacturing process is divided into five different steps. In the sole T4 softgel capsule available thus far, T4 is first dissolved in glycerine and then injected into a gelatin shell. This outer shell protects the active ingredient from degradation.

The brand liquid preparation of T4 is a 20-mL bottle containing 100 μg/mL sodium T4, with each milliliter equal to 28 drops, and each drop containing 3.57 μg of sodium T4 (21). Drops are to be dissolved in water and swallowed. Excipients are ethanol and glycerol (21). Noticeably, the Food and Drug Administration approved an alcohol-free oral solution in February 2017. Bernareggi *et al.* (22) demonstrated the stability of this T4 oral solution when added to breakfast beverages. The bioequivalence of these alternative T4 formulations has been accurately described (21, 23). Concerning tablet T4, which represents the choice treatment for hypothyroidism

Table 1. Excipients in T4 Tablet Formulations

	Tablet, Brand							Tablet, Generic			
	1	2	3	4	5	6	7	8	9	10	11
Cellulose	√	√		√	√		√			√	
Talc		√				√	√				
Povidone				√		√					
Colloidal silicone dioxide		√								√	
Starch		√	√			√	√	√	√	√	√
Acacia						√		√			
Gelatin			√								
Magnesium stearate ± stearic acid	√	√	√	√	√	√	√	√	√	√	√
Sodium croscarmellose	√		√		√						
Sodium citrate							√	√			
Sodium carboxymethylamide							√				
Calcium phosphate				√			√				
Calcium sulfate					√						
Bicarbonate					√						
Lactose	√		√			√		√	√		√
Dyes (color additives)	√				√	√					

Tablet, Brand: 1, Bagothyrox (Quimica Montpelier); 2, Eltroxin (GlaxoSmithKline); 3, Euthyrox (Merck); 4, Levothroid (Forest/Sanofi Aventis); 5, Levoxyl (Jones/King Pharmaceuticals); 6, Synthroid (Abbott); 7, Tirosint (IBSA Farmaceutici Italia). Tablet, Generic: 8 (Mercury); 9 (Almus); 10 (Sandoz); 11 (Actavis).

worldwide, there was a concern about switching between brands, from a brand to a generic preparation and from a generic to another generic. In 2008, the Endocrine Society published a position statement on this issue to ensure pharmacologic homeostasis of patients (see www.endocrine.org/advocacy/priorities-and-positions/bioequivalence-of-sodium-levothyroxine). There is, however, general consensus that switching between different tablet T4 preparations should be avoided (2, 9).

How Oral T4 Is Ingested

The T4 tablet is the most used preparation to treat hypothyroidism worldwide (1, 2). Patient compliance is, of course, a key factor for the proper achievement of the T4 therapeutic goal. Nonadherence to medications is a major challenge in the management of T4 treatment. When patients do not take T4 regularly, or do not comply with timing in relationship to food ingestion, and fail to report such behaviors to the endocrinologist, the clinician may wonder about the cause of a persistently elevated TSH, despite a high T4 dose (14). The term T4 pseudomalabsorption has been used to describe this specific situation. Initially the clinician might suspect a decreased T4 gastrointestinal absorption (24), and an evaluation for diseases causing malabsorption, or for drug interactions, should be performed. Some authors suggest that an oral T4 absorption test (by giving a total amount of 600 to 2000 μg of T4) could be used to demonstrate pseudomalabsorption (4, 25, 26).

The tablet formulations of levothyroxine contain a stable salt, sodium T4, together with a variety of excipients (27). After ingestion, a dissolution phase of the tablet is necessary for the subsequent intestinal absorption and, in the dissolution phase, a near physiologic gastric pH is required (28). After dissolution, and disregarding a hypothetical minimal absorption in the stomach, T4 is essentially absorbed in the small intestine (29, 30). Wenzel and Kirschsieper (31) showed that the absorption of T4 is significantly reduced when the drug is taken after a meal. Indeed, it has been shown that certain foods or drinks (*e.g.*, dietary fibers, soybeans, coffee, or papaya) (32–35) reduce the absorption of T4. Additionally, nonfasting regimens of T4 administration are associated with higher and more variable serum TSH concentrations (36). Under fasting conditions (in euthyroid subjects), the unidirectional absorption of T4 or peak values of T4 absorption occur in the first 90 minutes following T4 administration, with a rapid increase in the first 60 minutes (37). The time to reach the maximum concentration (T_{max}) of T4 is ~2 hours after T4 ingestion. Shortly afterward, absorption starts to plateau (37, 38).

On average, 60% to 80% of ingested T4 is absorbed and rendered bioavailable, with the distribution volume of the hormone averaging 11.5 L (37). However, in a study on hypothyroid subjects the T_{max} and distribution volumes were 3 hours and ~15 L, respectively (38). After a meal, the peak value of T4 absorption is decreased and T_{max} is delayed, with resulting decreased T4 bioavailability. When food is not postponed by at least 1 hour following T4 ingestion, delayed and decreased intestinal absorption of T4 may follow (37). However, bedtime intake of T4 significantly improved thyroid hormone efficacy, probably because the lower intestinal motility at night increases the exposure time of T4 to the intestinal mucosa (39) or because of better patient compliance with the treatment (40). Based on these results, postponing breakfast by 1 hour after ingestion of T4 has been suggested in different studies (28, 36, 40) to warrant efficient absorption of T4 and to carry out proper studies on malabsorption (41). In fact, in the latter studies the daily dose of T4 required to obtain a serum TSH between 0.5 and 2.5 mU/L was 1.3 μg/kg body weight (42, 43). This dose is significantly lower than the one recommended by an *ad hoc* American Thyroid Association task force (1.6 to 1.8 μg/kg body weight) in adult patients with minimal endogenous thyroid function (4). Despite these studies, leaflets on this hormone still indicate a lag time of 30 minutes between the morning ingestion of T4 and breakfast, and the same interval is commonly recommended by the prescribing physicians. Weekly tablet T4 administration has also been proposed (44), suggesting that autoregulatory mechanisms may maintain near-euthyroidism. However, for complete biochemical euthyroidism, a slightly larger dose than sevenfold the normal daily dose may be required (44). Presently, weekly tablet T4 administration is used only to detect nonadherence to treatment.

How Oral T4 Is Absorbed

The daily dose of T4 required to obtain the therapeutic effect is not a linear function of the ingested dose of T4, which is the main, but not only, decisive event. Various studies since 1933 investigated the percentage of oral T4 absorbed in humans with different techniques: a single isotope in feces, plasma, and liver; a double isotope; or using stable T4 and calculating the maximum increment in serum T4 or the area under the curve (AUC) after serial plasma T4 measurement (45). In these studies, in which patients had been treated with a different dosage and vehicle of oral T4, the percentages of T4 absorbed had been estimated between 17% and 93% of the ingested dose with an overall value of 60% to 80% confirmed in a study published in 1991 using ^{131}I-labeled T4 in three volunteers (mean value, 71% ± 3%) (30). These data have been confirmed, also using nonlabeled T4, by more recent studies (37). This value seems to be increased in patients with overt hypothyroidism; however, this is still a debated issue (38, 46). Some life conditions may be associated with variations in the absorption rate of T4. In particular, during pregnancy, the rise in progesterone leads to delayed gastric emptying and prolonged small bowel transit time by ~30% to 50% (47). This change may contribute to the overall increased need for T4 during pregnancy (48). Also, in geriatric age, the absorption of T4 seems to be slightly reduced. In fact, a decrease of tablet T4 bioavailability of ~4% by 10 years of age increase has been shown, suggesting that the percentage of T4 absorption is decreased in the elderly (49, 50). However, this issue has been recently questioned in an extensive study that failed to identify an effect of age on T4 requirement, suggesting that the decrease in lean body mass observed in elderly may be more likely responsible for these age-related changes in levothyroxine pharmacokinetics (51).

Levothyroxine sodium is absorbed along the whole small intestine with different percentages in its different segments: it has been shown that the mean values of labeled T4 absorption were 15% ± 5% in the duodenum, 29% ± 14% in the upper jejunoileum, and 24% ± 11% in the lower jejunoileum (30). A concomitant study of the mean transit time in the gastrointestinal tract revealed that it was 35 ± 30 minutes in the stomach, 7 ± 3 minutes in the duodenum, and 31 ± 8 minutes in the upper jejunoileum. The time between the oral intake and the appearance in the plasma seems to minimize the possibility of T4 absorption in the stomach. Once ingested, levothyroxine sodium in tablet formulation undergoes disintegration, deaggregation, and dissolution in gastrointestinal fluids (52); in fact, a prerequisite for successful absorption is that the active ingredient is in aqueous solution. Main factors affecting these processes are gastric juice pH and viscosity, type of excipients and structure, and shape and dimension of active ingredient particles (53). Furthermore, to ensure molecule stability and higher aqueous solubility, the pharmaceutical form is the sodium salt of levothyroxine: at 25°C, the aqueous solubility decreases as pH increases from 1 to 3, then reaches nadir values for pH between 3 and 7, and then increases again for pH >7 (54). Recently, a study about crystalline conformation of the sodium levothyroxine molecule revealed that it may exist in different polymorphs (different molecular conformations in the crystal form), which solubility changes at different pH values, showing a possible role of the different molecule conformations on T4 solubility (55). In the Biopharmaceutics Classification System, levothyroxine is recognized as a class III drug, that is, a high solubility drug with low intestinal permeability (56). However, it is important to underline that the solubility of a drug is tightly related to pharmaceutical formulation and may vary among the different preparations (57).

Transport of T4 Across the Intestinal Mucosa

In the early 1960s, it was thought that the transport of T4 inside cells occurred through passive diffusion mechanisms based on the high lipophilicity of the molecule (58). Since then, evidence has changed our understanding of the mechanisms underlying T4 transport. First, T4 is an amphipathic molecule with a lipophilic aromatic ring and a hydrophilic side chain and possesses three ionizable moieties, two acidic groups [phenolic (OH) and carboxyl (COOH)] and one basic group [amino (NH_2)]. The relative dissociation constants are 6.71, 2.04, and 8.85, respectively (59) (Fig. 1). Furthermore, it has been shown that at different pHs, the T4 molecule may exist at eight different microspecies (60). Additionally, it has been reported that the paracellular route of absorption may show only a negligible contribution for compounds larger than a molecular mass of 250 to 300 Da (61) and T4 is 774 Da. For these reasons, iodothyronines are trapped and not able to cross the lipid bilayer in the absence of specific carriers (62), and they become constituents of the cell plasma membrane in vertebrates (62). Besides the amphotericity of the molecule, further hindrance to diffusion through the plasma membrane comes from the charge of T4. In fact, in aqueous solution, T4 exists predominantly in ionized form and in particular in zwitterionic form (OH, NH_3^+, COO^-) in the range of pH between 2.46 and 6.91 and in monoprotonate form for more basic pH (O^-, NH_3^+, COO^-), whereas the cationic and anionic forms predominate at extreme pH (63). As a matter of fact, the pH-partition hypothesis postulates that "the absorption of ionizable drugs mainly takes place in compartment(s) where the local pH ensures a sufficient concentration of the noncharged form relative to the ionized form(s)" (64). Presently, therefore, these finding indicate the passive diffusion as a residual transport route (65).

Over time, studies have focused on the presence of specific carriers that facilitate the passage of thyroid hormones through the cell membrane. Different categories of transporters may act as a T4 carrier at the level of the small intestine: the monocarboxylate transporter (MCT) family, the organic anion-transporting polypeptide (OATP) family, the ATP-binding cassette transporter superfamily, and the large neutral amino acid transporter family (66).

Two MCTs involved in T4 transport have been identified in the small intestine mucosa: In fact, MCT8 and MCT10 mRNAs are expressed in both the stomach and small intestine human mucosa (67). Both of these transporters are constituted by 12 transmembrane domains with the amino-terminal and carboxyl-terminal intracellular domains, showing a high degree (49%) of homology of the amino acid sequence (65). Both transporters are responsible for cellular influx and efflux of T4 (68). MCT8, the primary transporter of thyroid hormone, is expressed in many tissues but its activity is mainly devoted to thyroid hormone transport across the blood–brain barrier and to the development of human brain, as proven by neurologic deficits in patients with MCT8 gene mutations (69). A specific localization of MCT8 in human intestine has not been identified, and the possible functions have not been extensively studied. However, its involvement in T4 transport has been suggested by the increased need for T4 observed in athyreotic patients treated with sunitinib and imatinib, which noncompetitively inhibited this transporter *in vitro*, perhaps by direct binding (70). On the contrary, MCT10 is highly expressed at the small intestine level and in particular in the basolateral membrane of mucosal cells, leading to the hypothesis of its possible role in the intestinal T4 resorption (65). Some members of the OATP family able to transport T4 have been identified in the small intestine. OATP1A2 has been identified in the apical brush border of duodenum enterocytes but in a small quantity (71, 72). This transporter carries a wide spectrum of substances in a Na^+- and ATP-independent way (73), but its

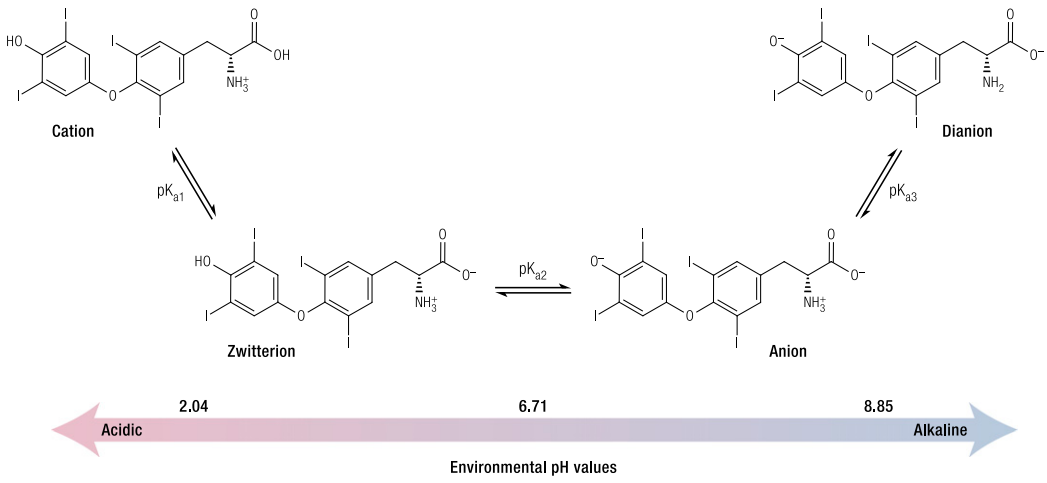

Figure 1. Different ionization status of the three ionizable moieties of the T4 molecule at different medium pH. pK_{a1}, ionization constant of the carboxyl group; pK_{a2}, ionization constant of the phenolic group; pK_{a3}, ionization constant of the amino group. [© 2019 Illustration Presentation ENDOCRINE SOCIETY]

activity may be sensitive to medium pH (74). The study of interferences on OATP1A2 activity allowed defining its importance for the transport of different compounds, including T4: in particular, flavonoids such as naringin and hesperidin, components of grapefruit and orange juice, respectively, may interfere with OATP1A2 (75). A study on the effect of naringin on OATP1A2 showed that its effect in reducing oral availability of these transporter substrates (*e.g.*, T4, acebutolol, fexofenadine) lasted 2 to 4 hours. The extent of that effect was different for each substrate and was more pronounced when the drug was hydrophilic and excreted unchanged and less when the drug was lipophilic and largely metabolized (75). It is not surprising that inhibition of OATP1A2 had only a minimal effect on the AUC of T4 (35). The authors postulated an effect on T4 elimination from enterocytes, and not on T4 absorption, that may impair hormonal enterohepatic recycling and thus bioavailability (35). The evidence that beta-blockers and tricyclic antidepressants may use this same transporter sheds light on a novel site of interaction with T4 (76). A similar involvement in the process of recycling of thyroid hormones from ileum to the liver has been proposed also for OATP4A1, through the portal vein (77). In a recent study, Meyer Zu Schwabedissen *et al.* (78) examined the role of OATP2B1 in contributing to intestinal T4 absorption. They concluded that thyroid hormones are, at the same time, substrates and transcriptional regulators of this transporter in enterocytes (78). P-glycoprotein is a membrane protein that belongs to the superfamily of ATP-binding cassette carriers that transports monodirectionally multiple substrates, including T4, out from cells (79, 80). The inhibition of this protein seems to be related to the increased AUC of levothyroxine when coadministered with rifampin (81). Large neutral amino acid transporter 1, which when associated with CD98 transports T4, has also been detected in Caco-2 cells, a model expressing many morphofunctional characteristics of the absorbent epithelium of the small intestine (82). However, the rate of T4 uptake was low (83). Overall, the existence of a main or T4-restricted transporter at the intestinal level is still an unanswered question. Moreover, it appears that substances and drugs impairing the activity of known intestinal T4 transporters mainly interfere with the outflow of the hormone from the enterocyte and with the enterohepatic recirculation of T4. In fact, once absorbed in the small intestine, T4 reaches the target organs where its peripheral metabolism takes place. Beyond deiodination, there are also alternative metabolic pathways, as extensively reviewed by Visser (84) and Wu *et al.* (85). In the liver, T4 and T3 are conjugated with sulfuric and glucuronic acid, which makes them more soluble, allowing their renal and biliary clearance (84). The presence of the intestinal microbial flora allows the binding of iodothyronine, thus creating a hormonal reservoir (85); alternatively, owing to the presence of sulfatase (86) and glucuronidase (87) activities in the intestinal contents, intestinal microbiota help their deconjugation and possible hepatic reuptake through portal circulation. Changes in the intestinal microbiota, known as dysbiosis, may therefore be responsible for variation in these metabolic steps (88, 89).

Gastric Disorders Affecting T4 Absorption

Plenty of conditions, either physiological, nutritional, pharmacologic, or pathologic, may impair the intestinal absorption of oral levothyroxine (2, 3). However, an increased need for T4 does not necessarily indicate gastrointestinal malabsorption of the hormone. Whether the serum TSH would be a reliable marker of hypothyroidism is still a debated issue (2, 90). However, in clinical practice, serum TSH levels are the easier and faster diagnostic tool to evaluate T4 treatment effectiveness (1, 2, 4).

In the past, uncertainty about the appropriate T4 dose for treatment of hypothyroidism, for both the general population and its relevant subclasses (*i.e.*, children, adults, elderly persons, obese, pregnant, polypharmacy, thyroidectomized), did not help to focus on T4 malabsorption. The more recent efforts to standardize T4 treatment (for reviews, see Refs. 1, 2, 4) and the seminal paper from Santini *et al.* (91), indicating that the dose of T4 is dependent on lean body mass, opened the door to more precise posology of T4 dose. Presently, the use of an individually tailored dose of T4 is advised to detect an increased need for T4 (41, 92).

Because there is no evidence that T4 may be significantly absorbed in places other than in intestinal sites, the observation that in patients with impaired gastric acid secretion a higher dose of T4 would also be required widened the research on T4 malabsorption mechanisms (28). Possibly confused with pseudomalabsorption in the past, the gastric-related malabsorption of levothyroxine currently represents an increasingly recognized issue in a relevant number of patients with hypothyroidism (41). The acid-producing machinery (*i.e.*, H^+/K^+ ATPase) is located in the oxyntic glands in the gastric fundus, and its action is enhanced by the production of gastrin from antral G cells (93). Acid production is partially or totally abolished in patients with chronic gastritis and/or gastric atrophy (94), and it is blocked in those treated with proton pump inhibitors (PPIs) (93) as well as partially blocked and counteracted by NH_3 production in patients with *Helicobacter pylori* infection (95, 96). All of these conditions have been related to increased T4 requirement (3, 28, 97, 98) (Fig. 2).

Evidence *in vitro* and *in vivo* highlighted this novel role for the stomach in subsequent intestinal T4 absorption (41, 99). *In vivo*, the role of gastric acid secretion has been demonstrated in treated goitrous patients with impaired gastric acid secretion (28). In fact, the daily T4 requirement was increased by a third in patients with *H. pylori*–related gastritis and atrophic gastritis and was maximal in those

with both of these conditions (28). In keeping with these results, patients with hypothyroidism with positive anti–parietal cell antibodies (PCAs) showed an increased daily T4 requirement (100). These authors found an increase by 17% in PCA-positive as compared with PCA-negative patients, and such an increase was even higher (+32%) in those patients with proven atrophic gastritis. In T4-treated patients with recent *H. pylori* infection, a significant TSH increase has also been observed. Such an effect was counteracted by increasing the dose of T4, being only partially reversed by *H. pylori* eradication (28). Eradication of this infection, in fact, does not always reestablish the previous conditions of the mucosa, as an antritis or even a pangastritis may ensue with a possible evolution to gastric atrophy (101). *H. pylori* infection affects 30% to 50% of the general population worldwide (102), and the high prevalence of this sole disorder may potentially increase the need for T4 in a higher number of patients than in those with supposed pseudomalabsorption.

Drug interference at the gastric level

A third way to impair gastric acid secretion is by treatment with PPIs. First, the effect of omeprazole on T4 needs has been described in patients with goitrous in whom the concomitant use of these two drugs significantly increased serum TSH (28). The effect was reversed by increasing the dose of T4 by 37% or by discontinuing the use of PPIs. Similar results were obtained by Sachmechi *et al.* (103) using lansoprazole in patients with serum TSH >5 mU/L. In contrast, absorption kinetics of high doses of T4 seem to be unchanged by the concomitant ingestion of pantoprazole and esomeprazole for 1 week (104, 105). However, the effect of PPIs on pharmacologic thyroid homeostasis has been confirmed by the TEARS study (106). Noticeably, very recent data *in vivo* pointed out that the replacement dose of T4 is inversely correlated with gastric pH, supporting the hypothesis that variations in gastric juice pH, such as during PPI treatment, may affect T4 dose (107). Besides PPIs, other drugs seem to interfere in a pH-related fashion with T4 absorption (*e.g.*, antiacids, calcium salts), with their effect having been extensively reviewed elsewhere (11, 108). Despite that the adsorption of T4 would be the main mechanism of interference for most drugs (11), the role of gastric pH may be relevant for some of them (Fig. 3). Besides the abovementioned effect of drugs in reducing gastric juice pH, a further pH-dependent process may occur at gastric level (109). On this ground, the effect of calcium carbonate is a model. In fact, Singh *et al.* (109, 110) have shown that both acute and chronic ingestion of calcium carbonate reduces the bioavailability of T4. A similar interference was also evident when using different preparations of calcium (111). In a first study (109), a supplementation of 1200 mg/d for 3 months led to a reversible increase of serum TSH in two-thirds of patients. Interestingly, in the same study, a binding study revealed that at pH 2, but not at pH 7.4, a significant fraction of T4 was adsorbed to calcium carbonate in a dose-dependent way, preventing absorption at the intestinal level. Additionally, this interference with oral T4 was confirmed by evidence that calcium carbonate acutely reduces the main pharmacokinetic parameters of T4 absorption (110). Some nutrients seems to act through a similar cooperative mechanism to reduce the absorption of T4 (112, 113). Indeed, papaya fruit contains proteolytic enzymes, including papain, that decrease histamine-induced acid secretion; however, the authors suggested that papaya fibers might also bind T4 in the intestine (112). Very recently, Chon *et al.* (113) described that simultaneous milk ingestion decreases oral levothyroxine absorption. The pH of naive cow's milk is ~6.6/6.7 and it contains >1 g of calcium per liter, so it is not surprising that the pH-sensitive fraction of T4 absorption might be affected (113). At the same time, naive milk contains fat, proteins, and lactose that may maintain T4 in the intestinal lumen, preventing its absorption (29, 114).

The overall mechanism by which intestinal absorption of T4 may be impaired in hypoachlorhydric patients, however, remains unclear. Iodothyronines are themselves pH-dependent molecules (54). *In vitro* studies have been carried out, and in 1971 Gordon and Coutsoftides (115) indicated that blood pH may affect the partition between the intravascular and rapidly exchanging pools of T4. Centanni and Robbins (116) have shown that the roles of pH in thyroid hormone uptake in skeletal muscle and several membrane transporters of T4 at the intestinal level are sensitive to pH changes (117). Besides naive T4, the pharmaceutical

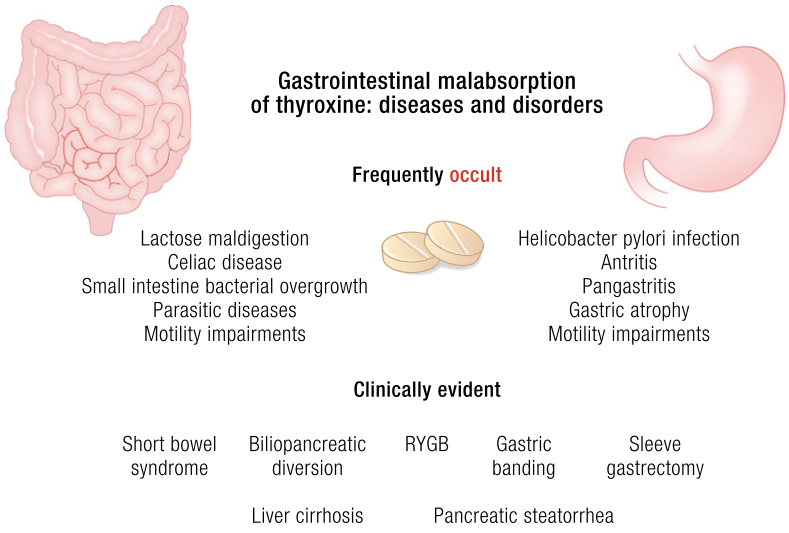

Figure 2. Main pathologic and postsurgical conditions leading to T4 malabsorption. Diseases have been subdivided based on the primitive site involved (stomach and intestine). [© 2019 Illustration Presentation ENDOCRINE SOCIETY]

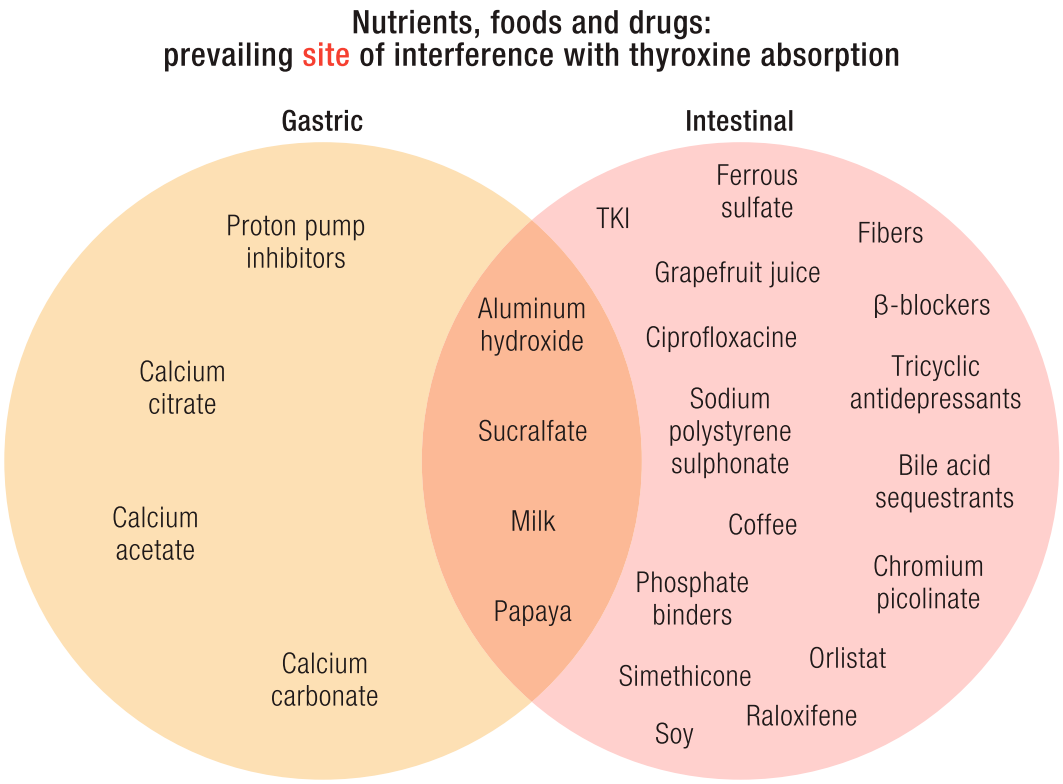

Figure 3. Nutrients, foods, and drugs interfering with T4 absorption. In the yellow circle: gastric level as the prevalent site of interference. In the red circle: intestinal level as the prevalent site of interference. In the orange overlapping part: interference exerted at both gastric and intestinal levels. [© 2019 Illustration Presentation ENDOCRINE SOCIETY]

preparation is also dependent on medium pH. Pabla *et al.* (99) have shown *in vitro* that the dissolution of tablet T4 is >85% within 20 minutes only at low pH (<2.4). According to the Food and Drug Administration, this time corresponds to the half-life of fasting gastric emptying for rapid-release drugs (57). At increasing medium pH the dissolution of tablet T4 rapidly decreases at all times studied (30, 60, and 120 minutes), whereas the softgel T4 preparation seems to be less sensitive to that variable (99). However, the dissolution time does not fully explain the subsequent absorption rate. In fact, Kocic *et al.* (118) have shown that the dissolution rate and the absorption rate in the first 2 hours may diverge, indicating that dissolution does not greatly influence the absorption of levothyroxine in the period of time (1.66 hours) in which the maximal absorption take place (37). Noticeably, a better absorption of T4 has been observed in patients simultaneously taking vitamin C (119, 120), which may lower gastric pH in patients with impaired acid secretion (108).

So far, it appears that the ionization status of T4 is important and that T4 ionizable moieties are dependent on ambient pH (121). It has been suggested that pharmaceutical T4 preparation, a hydrophilic sodium salt, may remain partly undissociated in a hypochlorhydric gastric environment, and this event may impair the efficiency of subsequent intestinal absorption (28). Although the mechanism is not completely elucidated, the clinician must be aware of the widespread impact of these interfering conditions because of the very high prevalence of *H. pylori* infection (102) and the prescription rate of PPIs (122). Therefore, in the past, studies aimed at identifying an appropriate daily T4 dose may have been biased from the presence of an unknown number of infected patients in the sample.

Altered gastric motility and bariatric restrictive procedures

Gastroparesis is defined as delayed gastric emptying in the absence of mechanical obstruction, and its prevalence is ~0.04% in an area of United States (123). Idiopathic, postsurgical, and diabetic gastroparesis are the most frequent forms. Only a few case reports deal with the correlation between gastroparesis and T4 absorption (124, 125). The first one described an old man with persistent hypothyroidism despite a high T4 dose (>2.7 μg/kg/d). In this case, upon exclusion of the main causes of T4 malabsorption, the diagnosis of gastroparesis had been confirmed by a gastric emptying study (124). In the second report, in a pregnant hypothyroid young female with type 1 diabetes, gastroparesis was diagnosed (125). In this study, the link between T4 malabsorption and gastroparesis was confirmed by a faint response of FT4 during a T4 absorption test. On the contrary, the weekly intramuscular injection of T4 led to the improvement of the thyroid hormonal profile. In addition to

gastroparesis itself, the residual food in the patient's stomach, which may adsorb the ingested T4, might represent a further mechanism of malabsorption (31, 125). In this patient, the refractoriness to oral T4 treatment worsened during the pregnancy because of an even slower gastric motility, which might have been induced by progesterone (126). Reardon and Yoo (127) also reported a better performance of softgel T4 preparation in a hypothyroid patient with gastroparesis, who quickly corrected her thyroid function by using that formulation of T4. A recent case report suggested that the motility of the whole gastrointestinal tract may affect T4 bioavailability (128). In fact, a severe refractory hypothyroidism was associated with systemic sclerosis, a chronic disorder characterized by muscular atrophy and fibrosis of the gastrointestinal tract. In this case, the esophageal sclerosis reduced esophageal motility, impairing the bolus progression of T4 (128). The authors suggested that the severe hypothyroidism was due to reduced T4 absorption, because TSH was progressively normalized upon switching to a liquid formulation of T4.

With regard to bariatric procedures involving gastric restriction (gastric banding and sleeve gastrectomy), they are considered procedures that alter drug absorption less than procedures involving intestinal diversion (129). The two mechanisms involved are drug disintegration and drug dissolution: the first step is necessary for a drug to become soluble within the gastrointestinal milieu and is the rate-limiting step in the absorption of most solid drug forms because the gastric mixing promotes drug disintegration (52, 53). In sleeve gastrectomy, a substantial part of the gastric fundus and body, the areas of the stomach containing most of the acid-producing cells, is removed. Therefore, the gastric pH increases and the solubility of some drugs would be reduced (129). Despite an expected increased need for T4 following bariatric surgery, the data are conflicting. Pharmacokinetic parameters of levothyroxine were, in fact, not decreased but rather increased in obese euthyroid patients before and after sleeve gastrectomy and gastric bypasses (130). In this study, however, the patients underwent T4 absorption tests with an oral solution of levothyroxine that does not require gastric dissolution (130). Aggarwal *et al.* (131) have analyzed 19 patients with hypothyroidism that underwent sleeve gastrectomy and demonstrated that 13 of 19 patients improved their thyroid status with a lower dose of T4, showing a correlation between percentage excess of weight loss and the change in T4 dose. Oppositely, Sundaram *et al.* (132) and Fierabracci *et al.* (133) demonstrated a decrease or no change in total T4 dose but an increase of weight-based levothyroxine requirement in patients after sleeve gastrectomy or gastric banding. To explain these contrasting results, authors have, time by time, suggested an accelerate gastric emptying, a modified gastrointestinal motility, the alterations in bile acid or in gut microbiome composition but without consistent data. The changes in lean body mass following bariatric surgery could also potentially contribute to a change in LT4 doses (91). In fact, only weight-based evaluation may lead to reliable results. Therefore, according to Gadiraju *et al.* (134), further controlled studies are needed before drawing definite conclusions.

Intestinal Disorders Impairing T4 Absorption

Celiac disease (CD) has an estimated prevalence in the general population of 1% (135) but its prevalence rises to 2% to 5% of patients who also bear a thyroid autoimmune pathology (136), the main cause of hypothyroidism. Furthermore, with thyroid autoimmune disease being the most frequent autoimmune disorder, a definite higher rate of Hashimoto's thyroiditis may be detected in patients with CD than in the general population (137). The joint presence of these two diseases is one of the more frequent associations included in polyendocrine autoimmune syndrome type 3B (138). The ratio between patients with overt CD and patients in whom the disease is present but not diagnosed is about 1:8 (139). As CD may also present without gastrointestinal-suggestive symptoms (CD atypical presentation) (139), its presence should be suspected in patients with hypothyroidism with an increased need for T4 (42). To our knowledge, the impairment of oral levothyroxine absorption in a patient with CD was first reported in 1993 in a patient with milk protein allergy and CD (140). Later, some case reports confirmed the occurrence of resistance to oral levothyroxine treatment in patients with hypothyroidism with celiac sprue (141, 142). In 2012, two studies (42, 143) elaborated the topic in 7 patients with untreated CD and in 35 subjects affected by atypical CD. In both groups, a gluten-free diet reversed the increased hormone needs, only partially in the first study (143) and completely in the second one (42). The mechanisms leading to the increased need for T4 in patients with CD may follow the progressive reduction of intestinal surface characterizing the histologic lesions of this disease: (i) villous shortening until total atrophy, owing to apoptosis of enterocytes and to inadequate cell regeneration in crypts (144), and (ii) significant lymphocytic infiltration. This event, in turn, determines the loss of proteins and enzymes in the brush border, thus impairing the absorption of a large number of nutrients (145). In patients with CD, the extent of impairment of drug efficacy may depend on the pharmacokinetic characteristics of each drug (146). In fact, besides reduction of the absorbing surface, the following pathologic characteristics were reported in patients with CD: increased intestinal permeability, increased gastrointestinal transit time, and changes in intestine luminal pH (146, 147). Abnormal gastric

emptying was even described, perhaps depending on an altered secretion of cholecystokinin and plasma polypeptide YY, hormones involved in gastrointestinal motility (147). Increased prevalence of bacterial overgrowth in the small intestine has also been observed, usually in patients with clinical persistence of symptoms, even after removal of gluten from the diet (148). Similar to other nutrients and drugs, all of these mechanisms may contribute to T4 malabsorption.

Lactose maldigestion is a condition, mostly symptomless, to which ~70% of adult human beings (lactase nonpersistent) are exposed (149). This condition is caused by the decline in residual lactase activity owing to the downregulation of the enzyme responsible for the hydrolysis of lactose to glucose and galactose (149). Lactose intolerance (LI) has instead a pleiotropic clinical picture, presenting with diarrhea, bloating, flatulence, abdominal pain, with the intensity of them being related to (i) the amount of lactose ingested, (ii) intestinal microbial composition, (iii) gastrointestinal motor activity, and, finally, (iv) the visceral sensitivity to fermentation products of lactose digestion (150). Besides the primitive form, LI may follow any process able to destroy the mucosa of the small intestine (*e.g.*, CD, infections, surgery) (151, 152). Initially, Muñoz-Torres (153) described a case of one patient showing an increased need for T4 induced by LI, resolved by switching to lactose-free T4 formulation and starting a lactose-free diet. A similar effect was observed following 8 weeks of lactose restriction, confirming that a lactose-free diet may improve thyroid pharmacologic homeostasis in patients with LI (154). Later, a systematic study confirmed the increased need for T4 in a larger group of patients with LI, as compared with a control group without signs or symptoms of malabsorption (+31%) (43). More than a mechanism may explain the effect of LI on the need for T4. When the hydrolysis of lactose does not take place, this sugar accumulates and attracts water in the intestinal lumen (150). Thus, an altered intestinal content may complex with T4, preventing absorption (43), or may even increase the intestinal motility, thus reducing the exposure of T4 to the absorbent surface (155). Moreover, LI is often associated with small intestine bacterial overgrowth (156), which may also impair the enterohepatic recycling of T4.

Lactose is also used as an excipient in some drugs and in some formulation of tablet T4, and the amounts are not often disclosed in the leaflets (27). This fact led to the suspicion that lactose content in these T4 preparations may represent a problem: a study, however, provided evidence that ingestion of up to 400 mg of lactose does not trigger gastrointestinal symptoms or affect the lactose breath test (157). Noticeably, gastrointestinal symptoms are usually evoked by quantities >5 g of ingested lactose (158). Therefore, the possibility that a very small amount of disaccharide in the T4 tablet might be responsible for its malabsorption is unlikely.

The parasitic infestation from *Giardia lamblia* has also been considered as a cause of T4 malabsorption. This parasitism is sporadic in Western countries where it seems more frequent in travelers (159). On the contrary, this flagellate protozoan is usually endemic in environments characterized by poor sanitary conditions (160). Clinical manifestations range from severe gastrointestinal derangement to asymptomatic forms (161). Only two case reports have described an increased need for T4 due to *G. lamblia* infestation (162, 163), both describing an elevation of serum TSH and an increased need for T4 that were reversed by appropriate antiparasitic treatment. The cause of T4 malabsorption in these patients is the inflammatory mucosal damage and epithelial apoptosis induced by the protozoan (164); furthermore, in these patients an increased intestinal permeability may be observed owing to the disruption of the intestinal tight junctions (165).

Besides the disorders directly affecting the absorbent mucosa, diseases affecting organs involved in the digestive process may impair oral T4 efficacy. Indeed, pancreatic insufficiency may cause steatorrhea following the reduction of lipase secretion at <10% of normal levels (166). In an early study on eight patients published in 1962 (167), the authors observed that pancreatic steatorrhea increased the elimination rate of the hormone, showing that fecal losses of the hormone were higher than normal. They hypothesized a defective hydrolysis of glucuronated T4 that impaired the enterohepatic circulation in these patients. A direct interference with compounds usually degraded by pancreatic enzymes, resulting in an organic iodine adsorption in the intestinal content, was also suggested (167). Cystic fibrosis that frequently leads to pancreatic insufficiency has been reported as a cause of decreased thyroid hormone absorption (168). Furthermore, a recent paper described two cases in which an increased need for T4 has been shown in patients bearing liver cirrhosis (169). The authors speculated that impaired bile secretion, besides the variation in thyroxine-binding globulin concentration, might explain this effect. Similarly, a study by Sinha and Van Middlesworth (114) underlined the role of bile in reducing the binding of T4 to intraluminal plasma proteins, thus increasing the absorption of labeled T4 in a washed jejunal loop of rats. The authors postulated the presence in the bile of substances competing for T4 binding with plasma proteins (114).

In a previous section, we described the putative mechanism of T4 absorption at the small intestine level; the effect of short bowel syndrome on T4 absorption has been investigated since the 1980s (170, 171). This disease is usually the consequence of congenital malformations or acquired diseases that require surgical resection of small intestine, thus

"A tight schedule of T4 treatment represents a prerequisite to detect any increased need for thyroxine."

causing reduction of the intestinal absorptive surface along with motility disturbances (172). Moreover, absence of the last ileal loop and of the ileocecal valve may lead colonic bacteria to rise in the residual small intestine, producing a dysbiotic environment dominated by *Lactobacilli* (173). The study of radiolabeled T4 absorption in five patients with short bowel syndrome as compared with two healthy subjects revealed a net reduction of oral T4 absorption independent from the lengths of intact bowel (170). It has been suggested that besides the shortened intestinal surface, a key role in determining T4 malabsorption in these patients may be played by the accelerated intestinal transit (174).

Bariatric surgery

On similar grounds, the interference on T4 absorption exerted by bariatric surgery, including intestinal bypass, has been extensively analyzed, although with conflicting results (see above for bariatric surgery involving only the stomach). The three case reports on effects of the jejunoileal bypass technique consistently reported a significantly (from threefold to fourfold higher than the normal dose) increased T4 need, again suggesting the role of a reduced absorptive surface (175–177). This technique was abandoned because of the association with multiple severe short-term and long-term complications. Currently, most of the papers published on this topic examined the need for T4 in patients who underwent Roux-en-Y gastric bypass (RYGB), a common procedure. By examining 23 patients, Raftopoulos *et al.* (178) observed that 13 of them maintained the same daily requirement while 8 showed a reduction of the dose. However, as mentioned above, Sundaram *et al.* (132) and Fierabracci *et al.* (133) described that, when normalized by weight, an increased T4 dose is necessary to achieve target TSH levels in most of these patients. These results are in keeping with the increased TSH values observed in patients treated with the same dose of T4 before and after surgery (170, 180). Two pharmacokinetic studies have been performed to investigate this issue (130, 181). Despite an improvement of absorption parameters, Rubio *et al.* (181) observed a significant delay of T4 absorption in the surgically treated patients. In the previously mentioned study (130), the pharmacokinetic parameters were similar before and after RYGB surgery. This latter study also examined 15 patients who underwent biliopancreatic diversion, observing an improvement of T4 pharmacokinetic parameters (130). However, Fallahi *et al.* (180), by using the same dose of tablet formulation of T4 before and after surgery, observed that serum TSH worsened after surgery. Although the results in patients exclusively treated with malabsorptive procedures agreed in identifying a clear increase in the T4 requirement, results about T4 needs in patients treated with procedures combining restrictive and malabsorptive techniques are conflicting. This may depend on the different schedule of T4 ingestion (often omitted) (*i.e.*, the lag time between food and therapy or other drugs) and on the diverse effects that surgery may have on a patient's gastrointestinal physiology (*e.g.*, altered gastric juice acidity, dumping syndrome, delayed gastric empting, different gut microbial flora, variations of lean and fat body mass ratio) (182, 183). Moreover, the assessment of T4 needs not always normalized by weight does not allow a correct and complete comparison of the data. The heterogeneity of these studies in patients who underwent bariatric surgery with mixed restrictive and malabsorptive techniques does not permit drawing definitive conclusions about the net effect on T4 requirement.

Nutrients and food interference

In 1977, using a double isotope method, Wenzel and Kirschsieper (31) clearly demonstrated that the fasting condition ensures better T4 absorption than in a feeding state. Over time, several studies have examined the interference exerted by different kinds of foods on the steps that lead to levothyroxine absorption.

As early as 1957, Van Middlesworth (184) reported that cellulose- or bran-rich chow led to increased fecal loss of T4 in rats. In 1996, Liel *et al.* (185) demonstrated a nonspecific, dose-dependent adsorption of the hormone by wheat bran *in vitro*. This may explain the clinical findings of an increased need for T4 in 13 patients with hypothyroidism who had increased their fiber intake (185). Conversely, a succeeding pharmacokinetic study in eight healthy volunteers did not confirm a variation in the absorption rate of T4 ingested with calcium polycarbophil or psyllium hydrophilic mucilloid (186). The possible interference of fibers on the enterohepatic recycling of T4 more than a direct effect on absorption has been suggested (187, 188) and may help to interpret these data. In fact, a similar mechanism has been postulated for the interference exerted by soy ingestion in T4-treated patients. In this first report in humans by Pinchera *et al.* (189), an athyreotic cretin, fed soybean formula, showed a refractoriness to high doses of desiccated thyroid. Additional evidence included an increased fecal concentration of T4 and a higher fecal mass, so that they hypothesized an intestinal dysbiosis as a further cause of intestinal trapping of T4 (189, 190). Several studies on this topic have confirmed the effect of soy formula in hypothyroid infants (191–193), and one study reported a similar effect also in a thyroidectomized woman using soy protein supplement (194). In this latter case report, the efficacy of T4 treatment was regained when separating T4 from soy ingestion by 12 hours. A very recent pharmacokinetic study, performed in 12 patients on stable T4 treatment, demonstrated that bioavailability of T4 is superimposable in patients coingesting a fixed combination of soy isoflavones or

with a 6-hour interval (195). A case report also described the impairment of pharmacological T4 homeostasis in a thyroidectomized patient after 2 weeks of large amounts of papaya fruit consumption (112). After discontinuation of papaya consumption, the patients recovered the euthyroid state without increasing T4 dosage. Besides the effects on gastric acid secretion (see above), the authors hypothesized an effect on intestinal motility of a component of the fruit and an action on deconjugating bacterial enzymes that may increase fecal T4 loss (112). A recent paper (113) has directly reported the effect of concomitant 2% fat cow milk intake with T4 (see above), hypothesizing also an interfering role for milk proteins, based on evidence from *in vitro* studies by Hays (29) and Sinha and Van Middlesworth (114).

Even espresso coffee may cause refractory hypothyroidism. The concomitant ingestion of coffee was examined *in vivo* and *in vitro* by Benvenga *et al.* (33). The simultaneous ingestion of coffee and levothyroxine altered pharmacokinetic parameters, also delaying the time of maximal incremental rise of serum T4. The *in vitro* study confirmed that coffee acts as a weak T4 sequestrant (33). The putative effects on T4 transporter activity by grapefruit juice have been discussed above.

Drug interference

Several drugs interact with intestinal absorption of levothyroxine. In most cases, these drugs are able to bind levothyroxine, creating insoluble complexes that prevent successive T4 absorption process, but this kind of interaction has not been proven for all of them. Some of these drugs seem to affect different steps of T4 absorption. Some clinical reports stated that aluminum hydroxide, an active ingredient of antacid preparations, affects T4 pharmacological homeostasis (196). In particular, the impact of this drug on T4 absorption seems to involve both gastric and intestinal processes of absorption. In fact, besides the above-mentioned increase of gastric pH and the slowing of gastric empting, a nonspecific adsorption of T4 *in vitro* (20% of the 50 μg in the incubation system were removed by 1 mL of aluminum hydroxide) (197) may further hamper oral T4 efficacy. Conflicting results *in vitro* and *in vivo* where obtained with a further antacid, sucralfate. In fact, in an early *in vitro* study the binding of T4 by sucralfate in gastric acid medium has been shown (198). Later on, one pharmacokinetic study, carried out on healthy volunteers, demonstrated that sucralfate reduces the maximum T4 absorption of ~70% with a significant delay in the absorption process (199). However, two clinical studies failed to confirm these findings (200, 201). This issue deserves clarification by further studies. Conversely, the concomitant ingestion of ferrous sulfate has been proven to reduce T4 efficacy in patients with hypothyroidism (202–204). In fact, an *in vitro* experiment demonstrated that at pH 7.4 a ferric ion binds three T4 molecules in an insoluble complex (202). A seminal paper published in 1969 (205) demonstrated that also cholestyramine resin, used as a lowering cholesterol agent (able to bind bile acids and cholesterol metabolites in the intestinal lumen), is able to bind a large amount of T4 either at pH 1 or 9 *in vitro*. By using ^{131}I-labeled T4 in two patients, the authors demonstrated a twofold increase in stool and a concomitant reduction in urine radioactivity as compared with control values, thus proving a negative effect on T4 absorption (205). An interval of 5 hours from levothyroxine to cholestyramine ingestion was not at all sufficient to restore T4 absorption, and the authors suggested that cholestyramine may act as an inhibitor of hormonal enterohepatic recycling (205). Because of this specific activity, this drug has also been used to treat acute hyperthyroid patients (206–208). The ability to impair the pharmacokinetic parameters of levothyroxine has been described in two studies on a further bile acid sequestrant, colesevelam (209, 210). This drug has been proven to bind T4, *in vitro*, in an increasing fashion from a medium pH of 1.2 (similar to gastric pH) to a pH of 6.8 (simulating intestinal fluid) (209, 211). *In vitro* binding has also been proven for a cation-exchange resin, sodium polystyrene sulfonate (212). Also, this ability of sodium polystyrene sulfonate has been proven in both an acidic medium (pH 2) and a neutral one: the reduction of dissolved T4 in the supernatant was 93% and 98%, respectively.

For some drugs, despite that an *in vitro* binding study has not been performed, pharmacokinetic studies demonstrated a reduction of T4 absorption. This is the case for ciprofloxacin, sevelamer, chromium picolinate, lanthanum carbonate, and raloxifene. Coadministration of these drugs with 1000 μg of T4 in healthy subjects decreased the T4 AUC from 0 to 6 hours, ranging from 17% to 50% as compared with the one observed in the control test (81, 210, 213, 214). Finally, a possible interference of orlistat (215) and simethicone (216) with T4 absorption has been only mentioned in case reports.

Use of Malabsorption of T4 as a Tool to Diagnose Occult Gastrointestinal Disorders

A tight schedule of T4 treatment represents a prerequisite to detect any increased need for T4. Patients requiring a higher than expected dose of T4 to reach the target TSH may be encompassed in the definition "difficult patients" according to Ward (217). They are exposed to refractory hypothyroidism (3), but not all of them have gastrointestinal malabsorption. Once the existence of an increased need for T4 is ascertained, the physician must first exclude pseudomalabsorption, recent and significant weight, body mass index, and/or body composition variations, as well as the possibility

"Individualization of hormonal treatment helps in the detection of gastrointestinal T4 malabsorption."

of pregnancy. Then, a careful nutritional and pharmacological anamnesis should be carried out (Fig. 4). Once these issues have been positively excluded, and gastrointestinal disorders may be reasonably suspected, a diagnostic workup should be started (Fig. 4). The clinical background should help in the diagnostic strategy, particularly when refractory iron-deficient anemia is concurrently present (218): this kind of anemia is, in fact, often associated with *H. pylori* infection (219), CD (220), and atrophic gastritis, prior to pernicious anemia (218). Atrophic gastritis and CD are in turn frequently associated with autoimmune hypothyroidism in the type III polyglandular autoimmune syndrome (98, 137, 221, 222), even in young patients (222, 223). A previous or active *H. pylori* infection must be screened as a first line, as it is the most prevalent disorder (102). Either a ^{14}C-urea breath test or fecal *H. pylori* antigen detection and the measurement of antibodies against *H. pylori* should be performed (102). If positive, following the appropriate treatment, the involvement of gastric mucosa should be investigated by endoscopy with multiple biopsies (224). Once the *H. pylori* infection has been excluded, other possibilities should be investigated by measuring the anti-PCAs and fasting gastrinemia (225). High serum gastrin levels and the presence of anti-PCAs support the suspicion of an autoimmune gastric atrophy (226), and again performing endoscopy with multiple biopsies of the gastric body and antrum is strongly suggested (94). In the presence of iron-deficient anemia and/or abdominal bloating and pain and/or chronic diarrhea, CD deserves attention (135). The assessment of anti-transglutaminase antibodies and total serum IgA levels may help to diagnose CD (135) but, once again, only endoscopy may confirm or exclude the presence of this disease (226). If the suspicion concerns other intestinal disorders, the diagnostic workup should include some breath tests (lactose, glucose, lactulose) able to detect LI (228), bacterial overgrowth (229), and/or altered transit time in the gut (229), respectively. These breath tests have been considered reliable, useful, and safe tools in the diagnosis of carbohydrate maldigestion, being also the least invasive tools to diagnose small intestine bacterial overgrowth (230). Finally, a stool examination should be kept in mind when parasitism is suspected (*e.g.*, *G. lamblia*) (163). Many of the described gastrointestinal disorders may occur in a hidden or even occult way (Fig. 2). In this case, the diagnostic workup should be driven by the prevalence of each diseases, taking into account the patient's and his/her familial medical history. A successful diagnostic workup may uncover the vast majority of gastrointestinal causes of a poor response to T4 treatment, but it would also be useful to diagnose and treat these silent, but not harmless, gastrointestinal disorders. In this view, malabsorption of T4 may represent a tool to diagnose occult gastrointestinal diseases.

Alternative Pharmacologic Perspectives

Although the tablet formulation of T4 remains the gold standard in the treatment of hypothyroidism, hormone paraphernalia has evolved. The "difficult patient" as described by Ward (217) is probably more than an exception in the treatment of hypothyroidism. The most recent advance concerning T4 treatment stems from the growing attention to alternative oral formulations: the liquid preparation and the softgel capsule. The soft gel capsule contains, in an outer gelatin shell, T4 dissolved in glycerine (23). This structure warrants a rapid dissolution in the acid gastric environment (231). The liquid formulation is composed of T4, glycerin, and ethanol and its most important feature is that it does not require gastric dissolution (16). A two-way crossover, bioequivalence study in 84 healthy subjects has been carried out to compare T4 tablets, soft gel capsules, and oral solution (21). Mean pharmacokinetic parameters were not statistically different between these formulations; however, a faster absorption of T4 solution was observed probably because of the lack of the dissolution phase (21). It is beyond the scope of the present review to analyze in detail the advantages and disadvantages of alternative preparations of T4, which were, however, recently reviewed elsewhere (232). In the present review, we analyzed the studies concerning the possible use of these alternative preparations in patients with gastrointestinal disorders. In a prospective study in 31 patients with gastric-related T4 malabsorption, stably treated with tablet T4 preparation and switched to softgel T4, the effective dose of this latter preparation was significantly reduced in about two-thirds of patients (233). More recently, very preliminary data suggested that the switch from tablet to softgel T4 preparation at an unchanged dose improved TSH even in patients taking a pill 30 minutes before breakfast (234). Furthermore, the softgel T4 preparation helps to overcome the problem of coffee and/or PPI interference on tablet T4 treatment (235, 236).

The obvious and most important advantage of the liquid T4 solution is the possibility of administration in pediatric age (237–239) or in patients who are not able to swallow tablets or capsules (232, 240). In hypothyroid newborns and infants the daily T4 dosage is calculated according to age, and T4 tablets are usually crushed and given with liquids (238, 239). In these very young patients, liquid T4 formulation is easily managed and administered and may also be better absorbed than the tablet formulation (239). The European Society for Pediatric Endocrinology guidelines acknowledged this alternative treatment in pediatric age (241). In adult patients with hypothyroidism, some studies analyzed whether the restraints of tablet T4 treatment may be overcome by the use of this preparation, that is, whether the foods may interfere with liquid T4 absorption as they do with tablet

formulation (242, 243). A double-blind, randomized, placebo-controlled, crossover trial suggested that a liquid T4 formulation could be ingested directly at breakfast, potentially improving therapeutic compliance (243) by reducing one of the major issues in the treatment with tablet T4: the negative impact of breakfast on treatment efficacy (31, 36, 37, 40, 243, 244). Liquid T4 preparation was tested even in patients with gastrointestinal malabsorption. In fact, in a prospective observational study, the liquid preparation has been proven to overcome T4 malabsorption induced by the increased gastric pH due to PPI treatment (245) and by LI (246). Similarly, in a case series, it has been shown that oral liquid formulation might bypass the pH alteration due to atrophic gastritis in patients who were still hypothyroid when treated with tablet T4 (247). As discussed above, drug malabsorption is a potential concern after bariatric surgery. In a recent study, patients with hypothyroidism, well replaced with T4 tablets before surgery (13 RYGB, 4 biliary pancreatic diversions), showed increased TSH 3 to 8 months after surgery (180); the switch to liquid T4, at the same dose, significantly improved TSH values also in patients with biliary pancreatic diversions, confirming previous studies in patients submitted to RYGB (179).

Despite some encouraging results in patients with gastrointestinal malabsorption, the overall analysis of these studies revealed some limitations: the entire field deserves further systematic studies before drawing definite conclusions (248).

Conclusion

Gastrointestinal malabsorption of oral T4 is more frequent than previously reputed and may account

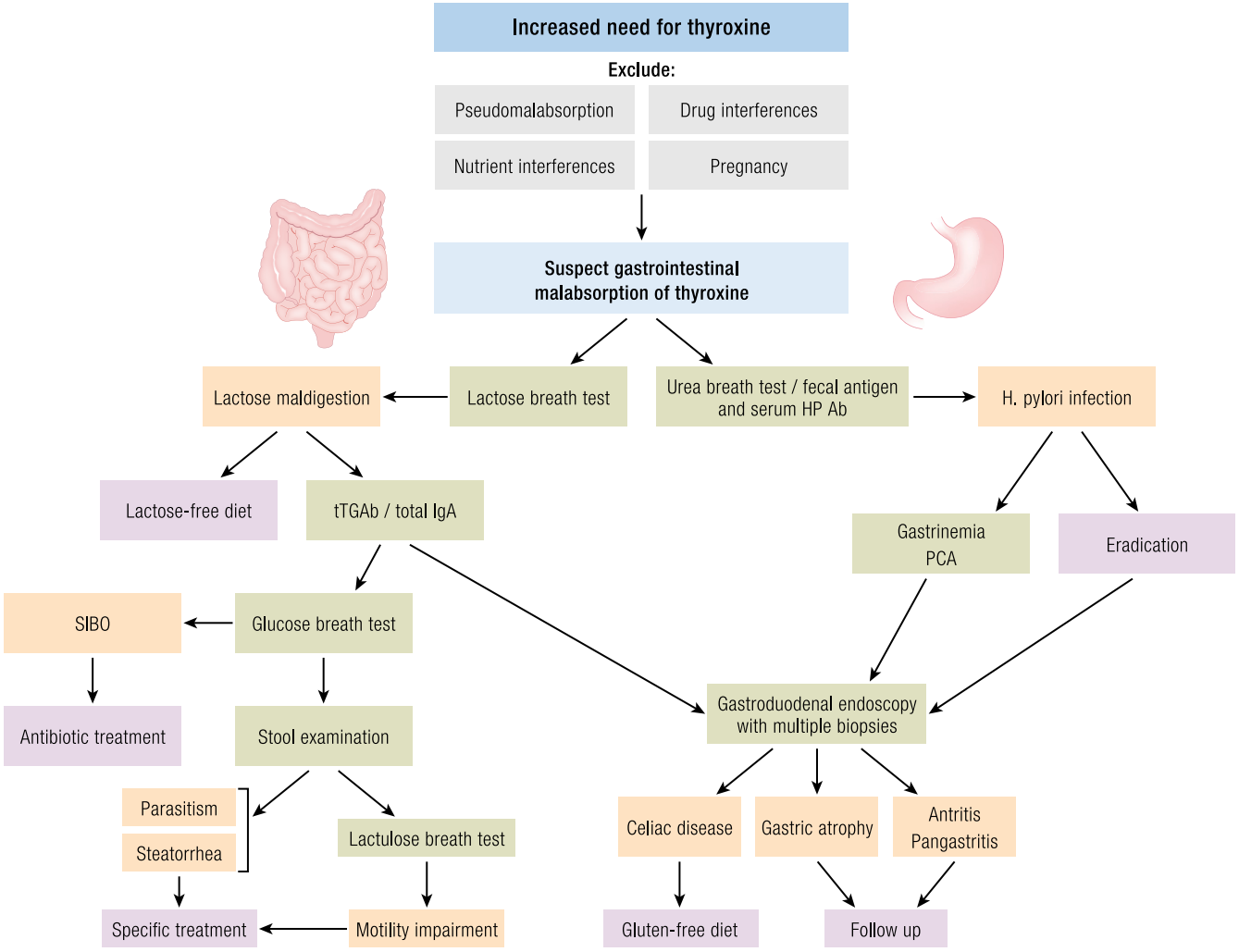

Figure 4. Diagnostic workup for the main pathologic gastrointestinal causes of T4 malabsorption based on the clinical ground and/or the prevalence of each disorder in the general population. Gray boxes include issues that must be excluded before starting a diagnostic workup. Orange boxes include diagnosed disease. Green boxes include diagnostic method. SIBO, small intestine bacterial overgrowth; tTGAb, anti-transglutaminase antibodies. [© 2019 Illustration Presentation ENDOCRINE SOCIETY]

for a significant fraction of refractory hypothyroidism. On this ground, an accurate individualization of hormonal treatment helps in the detection of gastrointestinal T4 malabsorption. Although the site of T4 absorption is the small intestine, gastric pH emerges as a major prerequisite for the efficacy of tablet T4 treatment. An increased need for T4 should induce the endocrinologist to start a diagnostic workup, based on the clinical features and on the prevalence of gastrointestinal disorders.

Despite the growing number of studies, some questions are far from being clarified. The pathophysiologic mechanisms of T4 absorption at the intestinal level are not yet completely defined, as shown by a number of patients in whom the cause of an increased need for T4 remains obscure. In particular, the intestinal transport pathways, the actual contribution of the enterohepatic recycling, and the role of microbiota composition in the absorption of T4 in humans are issues for future studies.

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Abbreviations

AUC, area under the curve; CD, celiac disease; MCT, monocarboxylate transporter; OATP, organic anion-transporting polypeptide; PCA, parietal cell antibody; PPI, proton pump inhibitor; RYGB, Roux-en-Y gastric bypass; T_{max}, time to reach the maximum concentration.