REVIEW ARTICLE

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Drug Effects on the Thyroid

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There is a growing list of medications known to adversely affect thyroid function or interpretation of the results of standard thyroid laboratory testing. Many of these drugs are commonly used preparations, ranging from over-the-counter supplements to advanced medical therapy, and include antiarrhythmic agents, antineoplastic agents, and glucocorticoids. The unintended consequences of pharmacologic therapy on the thyroid vary in importance from artifactual laboratory effects to severe thyroid dysfunction. This review provides a systematic approach to drug-induced thyroid dysfunction, with an emphasis on clinically relevant interactions and on artifacts on laboratory assays.

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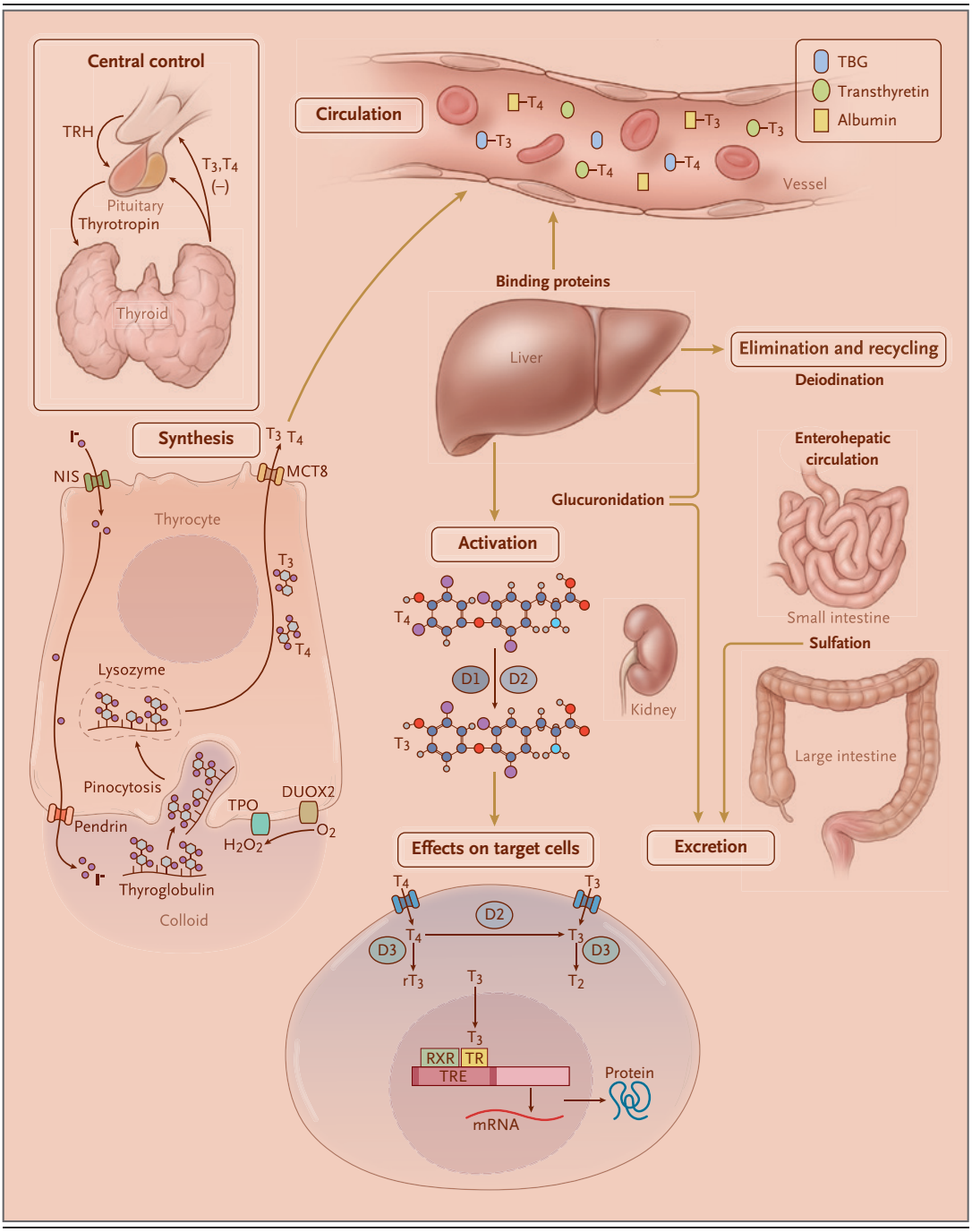
THYROID HORMONE PHYSIOLOGY

Knowledge of thyroid hormone physiology is useful in understanding specific drug interactions (Fig. 1). Thyrotropin controls all aspects of thyroid hormone synthesis and release. Secretion of thyrotropin is stimulated by thyrotropin-releasing hormone and inhibited by negative feedback through thyroid hormone. Iodide derived from dietary sources is transported into the thyroid against a concentration gradient by means of the sodium–iodide symporter and diffuses through follicular cells for transport into the follicular lumen by means of the anion exchange protein pendrin and possibly other channels.[2] Within the follicular lumen, iodide is oxidized and bound to specific tyrosine residues in thyroglobulin molecules through the activity of thyroid peroxidase. Iodinated tyrosine groups in thyroglobulin are coupled together to form either thyroxine (T_4) or triiodothyronine (T_3). Through pinocytosis, follicular cells respond to an increased thyrotropin level by ingesting luminal colloid within vesicles, which then fuse with lysosomes, leading to proteolytic release of T_4 and T_3 from thyroglobulin. Liberated thyroid hormone is exported to the systemic circulation through transporters such as monocarboxylate transporter 8.

One hundred percent of T_4 is produced in the thyroid, but 80% of T_3, the active form of thyroid hormone, is derived from the 5′-monodeiodination of T_4 in peripheral tissues such as the liver and kidney through the action of type 2 and type 1 deiodinase. More than 99% of circulating T_4 and T_3 is bound to serum proteins, including thyroxine-binding globulin, transthyretin, and albumin. Uptake of thyroid hormone into target tissues occurs through transporters from both the monocarboxylate transporter and organic anion-transporting polypeptide families. Within the nucleus, T_3 controls gene expression by binding to the thyroid hormone receptor, which forms a heterodimer with the retinoid X receptor and interacts with the thyroid hormone response element within thyroid hormone–responsive genes.[1]

Metabolism of thyroid hormone occurs primarily through sequential monodeiodination in numerous tissues, including the liver, kidney, thyroid, skin, and



placenta.[3] Additional pathways include glucuronidation and sulfation, with ultimate excretion in the bile and feces or urine. Glucuronidated thyroid hormone in bile can be deconjugated by gut bacteria and recycled through the enterohepatic circulation, a process that can provide a thyroid hormone reservoir.[3] Sulfation has the added effect of facilitating rapid deiodination by type 1 deiodinase. Intrathyroidal iodinated intermediates, including monoiodotyrosine and diiodotyrosine,

Figure 1 (facing page). Thyroid Hormone Physiology.
Hypothalamic–pituitary control of thyroid function is subject to negative feedback by triiodothyronine (T_3). Thyrotropin-releasing hormone (TRH), which is derived from paraventricular neurons in the hypothalamus, stimulates the release of thyrotropin from the pituitary thyrotroph. Pituitary T_3 is derived from both the systemic circulation and intrapituitary 5′-deiodination of thyroxine (T_4) by type 2 deiodinase. Thyroid hormone synthesis occurs within thyroid follicles, each consisting of hundreds of thyrocytes surrounding a follicular lumen filled with colloid matrix. Thyroglobulin produced in the thyrocyte is secreted into the follicular lumen, where it serves as a backbone for thyroid hormone synthesis. Iodide is actively transported into the thyrocyte through the sodium–iodide symporter (NIS) and then transferred to the follicular lumen through the anion exchange protein pendrin. In the lumen, iodide is oxidized and bound to specific tyrosine residues within thyroglobulin. This reaction, and the subsequent coupling of two iodinated tyrosine molecules to form T_4 or T_3, is catalyzed by thyroid peroxidase (TPO) in a reaction dependent on hydrogen peroxide, which is produced by dual oxidase 2 (DUOX2). Iodinated thyroglobulin is ingested by the thyrocyte through pinocytosis, allowing proteolysis within lysosomes to release T_4 and T_3, which are transported to the circulation through monocarboxylate transporter 8 (MCT8). Generation of T_3 largely occurs outside the thyroid, through 5′-monodeiodination of T_4 by 5′-monodeiodinase type 2 (D2) and 5′-monodeiodinase type 1 (D1). Although much of this activation occurs within the liver, kidneys, and skeletal muscles, numerous other tissues are capable of local conversion of T_4 to T_3. Circulating thyroid hormone is more than 99% bound to carrier proteins, including thyroxine-binding globulin (TBG), transthyretin, and albumin. The serum levels of albumin and transthyretin are much higher than the level of TBG, but the latter accounts for approximately 75% of binding because of its greater affinity for thyroid hormone. T_3 exerts nuclear effects on target cells throughout the body by binding to the thyroid hormone receptor (TR), which along with its heterodimeric partner, retinoid X receptor (RXR), binds to thyroid hormone response elements (TREs). Concurrent binding of coactivators or corepressors allows for positive and negative regulation of thyroid hormone–responsive genes. Diverse tissues exert local control over thyroid hormone action by converting T_4 to T_3 through the actions of D1 and D2 or by deactivating T_4 to rT_3 (reverse T_3) and T_3 to T_2 through the actions of D3.[1] Thyroid hormone is primarily degraded through successive deiodination. Conjugation of thyroid hormone, through glucuronidation and sulfation in the liver and kidney, increases its water solubility, allowing secretion in the bile. Whereas sulfated thyroid hormone is rapidly subjected to further deiodination and eliminated in the urine or feces, glucuronidated thyroid hormone may be either eliminated in the feces or deconjugated by gut microorganisms and recycled in the enterohepatic circulation.

Table 1. Classification of Drug Effects on the Thyroid.*

Interference with endogenous thyroid function
Disruption of hypothalamic–pituitary control
Decreased thyroid hormone production or release
Increased thyroid hormone production
Enhanced thyroid autoimmunity
Destructive thyroiditis
Changes in thyroid hormone–binding proteins
Inhibition of thyroid hormone activation (T_4-to-T_3 conversion)
Displacement of thyroid hormone from binding proteins
Increased thyroid hormone metabolism or elimination
Interference with thyroid hormone therapy
Decreased pill dissolution
Decreased thyroid hormone absorption
Decreased free thyroid hormone levels
Increased thyroid hormone metabolism or elimination
Interference with thyroid laboratory testing in euthyroid persons
Falsely elevated thyroid hormone levels
Falsely low thyroid hormone levels
Falsely low serum thyrotropin levels
Falsely elevated thyrotropin-receptor antibody levels

* T_3 denotes triiodothyronine, and T_4 thyroxine. For a detailed list of drugs interacting with the thyroid, see Tables S1 and S2 in the Supplementary Appendix, available with the full text of this article at NEJM.org.

undergo deiodination by iodotyrosine dehalogenase, resulting in the conservation of iodine for later thyroid hormone synthesis.

CLASSIFICATION OF DRUG EFFECTS ON THE THYROID

Each of the steps in thyroid hormone control, synthesis, release, transport, and metabolism is susceptible to drug interactions (Table 1 and Fig. 2). Several drugs or drug classes, such as amiodarone, glucocorticoids, and antiepileptic agents, interfere with the thyroid on multiple levels. Patients receiving thyroid hormone replacement therapy are susceptible to unique drug interactions that interfere with pill dissolution, gastrointestinal absorption, or metabolic clearance.

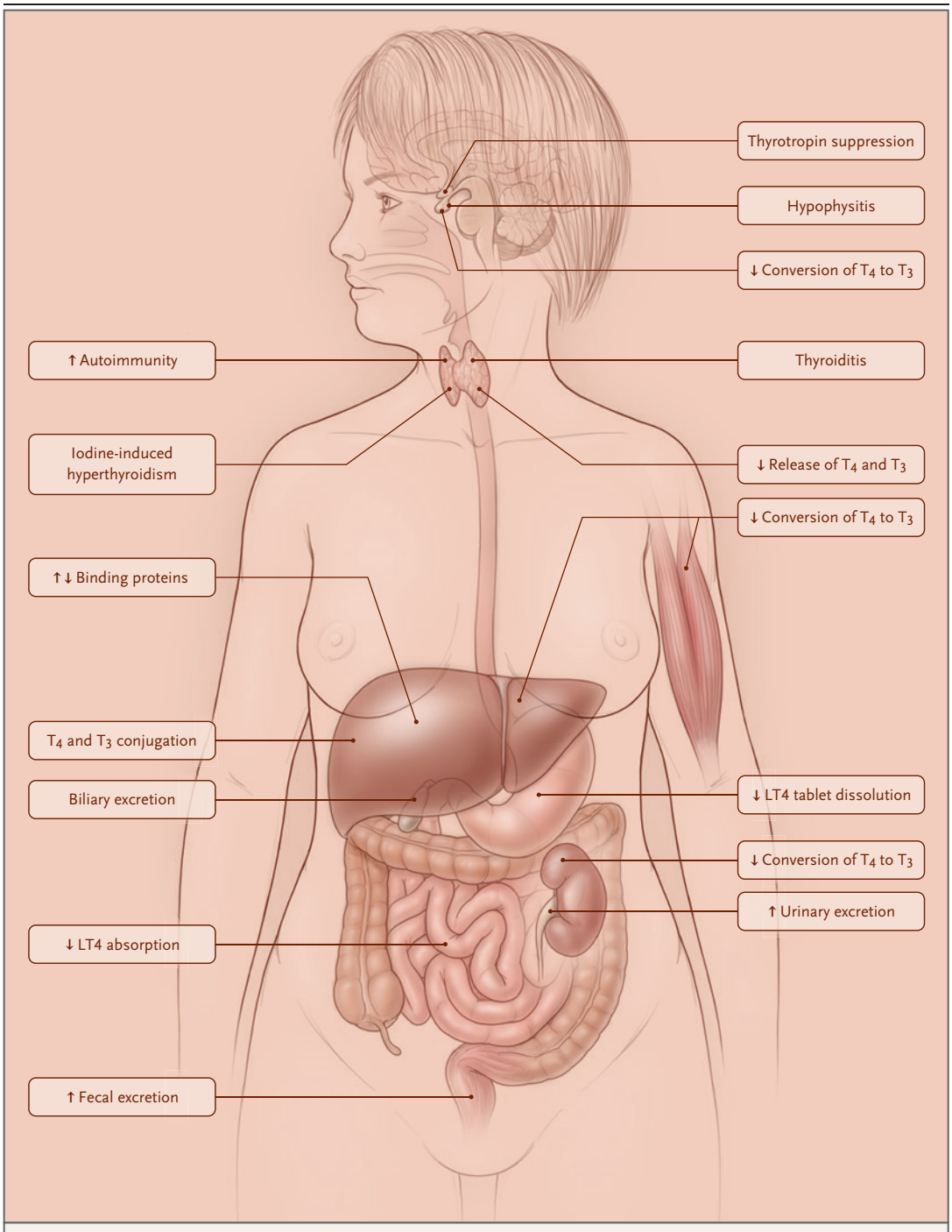


Figure 2. Anatomical Sites of Interactions between Drugs and Thyroid Function.

Multiple sites of interaction between various drugs and the thyroid have been identified, including central control at the pituitary–hypothalamic level, direct effects on thyroid hormone synthesis, initiation of destructive thyroiditis, interference with protein binding or delivery to target tissues, and interference with activation and disposition of thyroid hormone. Unique drug interactions occur in patients taking exogenous thyroid hormone, including inhibition of pill dissolution and levothyroxine malabsorption. LT4 denotes levothyroxine.

DRUGS AFFECTING HYPOTHALAMIC–PITUITARY CONTROL OF THE THYROID

The synthetic retinoid bexarotene induces rapid and profound thyrotropin suppression, leading to overt central hypothyroidism in 40 to 70% of treated patients, with recovery of normal function within weeks after drug discontinuation.[4,5] These effects occur through the direct action of bexarotene on pituitary thyrotrophs and are compounded by enhanced thyroid hormone metabolism through nondeiodinase pathways such as sulfation.[6]

Mitotane causes hypothyroidism in most patients treated for adrenocortical carcinoma.[7,8] Patients present with subnormal free T_4 levels, an inappropriately normal thyrotropin level, and a blunted thyrotroph response to thyrotropin-releasing hormone, findings that are consistent with central hypothyroidism.[7] Free T_4 levels begin to fall within the first 3 months of treatment with mitotane.[8] Long-term thyroid hormone replacement therapy is often required.[8]

Immune checkpoint inhibitors, including those that inhibit cytotoxic T-lymphocyte antigen 4 (CTLA-4) and programmed cell death 1 (PD-1) receptor, have a variety of adverse endocrine effects.[9] Hypophysitis occurs more frequently in patients taking CTLA-4 inhibitors, whereas primary thyroid dysfunction is seen more often with PD-1 inhibitors.[9] Ipilimumab, an anti–CTLA-4 agent, has been linked to destructive hypophysitis, with varying degrees of central hypothyroidism, adrenal insufficiency, and hypogonadism occurring in 3 to 10% of patients treated for melanoma at the approved dose of 3 mg per kilogram of body weight every 3 weeks for up to 4 cycles.[10-12] The effects occur within 1 to 3 months after the initiation of treatment (within 2 to 4 cycles). Affected patients present with headache, fatigue, weight loss, cold intolerance, and loss of libido. Magnetic resonance imaging reveals pituitary enlargement, pituitary-stalk thickening, and homogeneous enhancement in many but not all cases.[10,12] Recovery of gonadal and thyroid function is seen in up to one half of patients, whereas adrenal axis recovery rarely occurs.[9,10]

Several categories of drugs exert suppressive effects on thyrotropin release without appreciably affecting circulating T_4 levels, including glucocorticoids, dopamine agonists, somatostatin analogues, and metformin.[13,14] Although thyrotropin suppression in patients receiving these agents is usually metabolically insignificant, a low thyrotropin level with a normal free T_4 level may be confused with subclinical hyperthyroidism, prompting unnecessary evaluation or treatment.

DRUGS AFFECTING THYROID HORMONE SYNTHESIS OR RELEASE

Excess intrathyroidal iodine inhibits thyroid hormone synthesis, resulting in the Wolff–Chaikoff effect. Although the exact mechanism is unknown, acute inhibition of thyroid peroxidase may occur through the generation of intrathyroidal iodinated compounds such as iodolactones and iodoaldehydes.[15] Persons with a normal thyroid escape this effect within 1 to 2 weeks, but those with compromised thyroid function as a result of underlying lymphocytic thyroiditis or partial thyroid ablation with radioiodine or surgery may not escape this effect until the iodine load has cleared. Iodine excess also contributes to thyrotoxicosis (the Jod–Basedow phenomenon), particularly in patients with preexisting autonomous thyroid function.[16]

Common drug sources of excess iodine include iodinated contrast agents used for computed tomography and cholecystography, medications with a high iodine content such as amiodarone and topical povidone–iodine, and over-the-counter preparations and supplements, including expectorants, vaginal douches, and kelp. Amiodarone, a class III antiarrhythmic agent, is 37.3% iodine by weight and undergoes partial deiodination, releasing approximately 7 mg of iodide per 200-mg tablet,[17] which is roughly 45 times the recommended daily intake of 150 μg for men and nonpregnant women. In addition to inducing hypothyroidism in susceptible patients, iodine from amiodarone causes hyperthyroidism in some patients, a disorder known as type 1 amiodarone-induced thyrotoxicosis.[16] Other interactions of amiodarone with the thyroid are discussed below.

Lithium use causes goiter and hypothyroidism by decreasing thyroid hormone release through the inhibition of colloid pinocytosis. In a study involving patients with manic depression, 50% of those treated with lithium had a goiter on thyroid ultrasonography, as compared with 16%

of patients who did not receive lithium.[18] The reported prevalence of hypothyroidism among patients receiving lithium varies widely. A summary of 1778 published cases showed a mean prevalence of 17.6%.[19] A meta-analysis showed that the prevalence of hypothyroidism among lithium-treated patients was increased by a factor of 6 as compared with the prevalence among controls.[20] Risk factors include female sex and an age of more than 40 years, both of which cosegregate with chronic lymphocytic thyroiditis and a positive test for thyroid peroxidase antibodies,[21] indicating diminished thyroid reserve and increased autoimmunity as possible predispositions. Lithium use is also linked to painless thyroiditis.[22] Although the nature of this association is unknown, approximately half of affected patients have positive tests for thyroid antibodies.[22]

DRUGS THAT ENHANCE THYROID AUTOIMMUNITY

Newer drugs designed to promote immune system targeting of cancer cells also increase the risk of autoimmune disorders. Primary thyroid dysfunction is noted variably in the literature[23-30] as affecting approximately 5 to 10% of patients treated with CTLA-4 inhibitors,[23,25] 10 to 20% of those treated with PD-1 inhibitors,[26,27] and more than 20% of patients treated with combination therapy.[24,26] Most patients receiving such therapy for cancer have painless thyroiditis, presenting with transient thyrotoxicosis followed by hypothyroidism. Graves' disease rarely occurs. Thyrotoxicosis typically develops 4 to 8 weeks after the start of therapy[28] but may occur within 2 weeks with combination therapy[26,28] or by 18 weeks with anti–CTLA-4 monotherapy.[26] The thyrotoxic phase is often mild and may be overlooked, resolving in 3 to 10 weeks,[26] but moderate and severe cases have occurred.[29] Hypothyroidism ensues 10 to 20 weeks after the initiation of therapy[30] and is often irreversible.[9,30] Immune checkpoint blockade therapy is generally not stopped because of adverse thyroid effects,[26] which are managed conventionally.[16,31]

Thyroid dysfunction during immune checkpoint blockade is believed to reflect a reduction in immune self-tolerance caused by these drugs.[10,32] In 40 to 50% of affected patients, thyroid peroxidase or thyroglobulin antibodies are present at the time of thyroid disruption,[27,30] but their pathophysiological role is uncertain. Most series do not include pretreatment antibody levels. Some studies show increases in preexisting antibodies[33,34] or antibody development[35] during immune checkpoint blockade. A positive pretreatment test for antibodies indicates an increased risk of drug-induced thyroid dysfunction.[33,35] Additional mechanistic studies are required to better understand the adverse effects of immune checkpoint blockade on the thyroid.

The use of nonspecific immunostimulatory cytokines such as interleukin-2 and interferon alfa in patients with metastatic renal-cell carcinoma, melanoma,[36] or hepatitis C[37] results in thyroid dysfunction in 15 to 50% of patients, with varying degrees of hypothyroidism often preceded by thyrotoxicosis due to thyroiditis.[38] In a series of 89 patients with solid tumors treated with interleukin-2, thyroid dysfunction developed in 22% of the patients, manifested as mild thyrotoxicosis at a median of 7 weeks and subsequent hypothyroidism at a median of 11 weeks.[38] Thyroid antibodies developed in a majority of patients with negative antibody tests before treatment. Among 1233 patients with hepatitis C who were euthyroid before receiving interferon alfa, thyroid events occurred in 16.7% of the patients, including approximately 5% with thyrotoxicosis and 12% with hypothyroidism.[37] Mechanisms underlying cytokine-induced thyroid dysfunction are poorly understood, but risk factors for thyroid autoimmunity, including female sex, a positive test for thyroid antibodies at baseline or during treatment, and marginally normal baseline thyrotropin levels, are disproportionately present in affected patients.

Alemtuzumab is a humanized monoclonal antibody against the cell-surface antigen CD52. Treatment with alemtuzumab leads to a profound depletion of circulating B cells and T cells and a high rate of thyroid autoimmunity in patients with multiple sclerosis.[39,40] Among 248 patients who were treated with alemtuzumab, thyroid dysfunction developed in 41.1%, and Graves' disease developed in 71.6% of affected patients; the median interval between the final alemtuzumab dose and the onset of Graves' disease was 17 months.[40] Subacute thyroiditis and primary hypothyroidism are also seen with increased frequency after alemtuzumab therapy.[39] Most cases of alemtuzumab-associated thyroid

dysfunction are diagnosed within 3 years after the completion of therapy, but cases have occurred 5 to 9 years after drug cessation.[39,40] Graves' disease after alemtuzumab therapy is associated with a high rate of fluctuations in stimulating and blocking antibodies against the thyrotropin receptor,[40] an uncommon event manifested as alternating periods of hyperthyroidism and hypothyroidism.

In a phase 2 clinical trial of alemtuzumab in patients with multiple sclerosis, 15.1% of participants in whom thyroid dysfunction developed had positive tests for thyroid peroxidase antibodies at baseline and 54.8% had negative tests at baseline that became positive during treatment.[39] Notably, alemtuzumab use in patients with leukemia[41] or rheumatoid arthritis[42] has not been associated with Graves' disease, and use of another immunotherapy, interferon beta-1a, in patients with multiple sclerosis results in a comparatively low rate of thyroid dysfunction, at 6.5%.[39]

Mechanisms responsible for the occurrence of thyroid autoimmunity after alemtuzumab are not known. One interpretation of data on lymphocyte reconstitution after alemtuzumab therapy suggests that early B-cell recovery in the window preceding reemergence of regulatory T cells allows for enhanced B-cell–mediated autoimmunity.[43] Other examples of thyroid autoimmunity occurring after recovery of the immune system include Graves' disease after highly active antiretroviral therapy for advanced human immunodeficiency virus infection,[44] thyroid autoimmunity in patients who have been cured of endogenous Cushing's disease, and thyroid autoimmunity during the postpartum period.

DRUGS CAUSING DIRECT THYROID DAMAGE

Amiodarone causes a destructive thyroiditis, referred to as type 2 amiodarone-induced thyrotoxicosis, in 5 to 10% of treated patients. This disorder is believed to result from direct cytotoxic effects of amiodarone on thyrocytes.[16] Affected patients may present with persistent tachycardia or worsening arrhythmia, a nontender thyroid on physical examination, elevations in serum free T_4 and T_3 levels, and a suppressed serum thyrotropin level. Unlike type 1 amiodarone-induced thyrotoxicosis, which is typically managed with antithyroid drugs, type 2 disease is preferentially treated with glucocorticoids.[45] In practice, it is often difficult to distinguish type 1 from type 2 disease, and the urgent need for treatment in patients with a tenuous cardiac status often prompts clinicians to provide therapy initially with both antithyroid drugs and glucocorticoids.[16,46]

Targeted cancer therapy involving tyrosine kinase or multikinase inhibitors has been associated with an increased risk of thyroiditis.[47] The most widely reported changes occur in patients receiving sunitinib for metastatic renal-cell carcinoma or gastrointestinal stromal tumors.[47,48] In three large clinical trials, hypothyroidism occurred in 14 to 25% of patients with renal-cell carcinoma who were treated with sunitinib.[49-51] Most cases were rated as mild to moderate in severity, but there were rare cases of severe dysfunction. In a trial involving 42 patients with normal thyroid function before treatment with sunitinib, hypothyroidism occurred in 36% of participants, many of whom had thyrotropin levels greater than 20 mIU per liter.[48] The likelihood that hypothyroidism would develop increased with the duration of therapy. Forty percent of patients were found to have transient thyrotoxicosis before hypothyroidism developed, a finding that is consistent with destructive thyroiditis. The mechanisms contributing to the development of thyroiditis in patients taking tyrosine kinase inhibitors may be related to ischemia resulting from the inhibition of vascular endothelial growth factor receptor by several drugs in this class.[47] Marked thyroid involution has been noted ultrasonographically in some affected patients.[48]

DRUGS AFFECTING PROTEIN BINDING OF THYROID HORMONE

Several drugs lead to increases in thyroxine-binding globulin, including oral estrogen and selective estrogen-receptor modulators, methadone, heroin, mitotane, and fluorouracil. Conversely, reductions in this protein occur with the use of androgens, glucocorticoids, and niacin. The most common and clinically relevant changes in thyroxine-binding globulin occur with the use of estrogen-containing drugs in patients receiving thyroid hormone replacement therapy.[52] In such patients, increases in protein binding lead to additional binding of T_4, even in the presence of low free T_4 levels. Consequently, patients de-

Table 2. Drugs That Cause Spurious Thyroid Test Results in Euthyroid Persons.

Drug	Drug Class	Test Results			Condition Mimicked
		Thyrotropin	Free T_4	T_3	
Amiodarone	Class III antiarrhythmic agent	High end of normal range	High	Low end of normal range	Thyrotropin-secreting pituitary adenoma, thyroid hormone resistance
Biotin	Micronutrient	Low	High	High	Primary hyperthyroidism
Carbamazepine and oxcarbazepine	Antiepileptic agent	Normal	Low	Low end of normal range	Central hypothyroidism
Enoxaparin	Anticoagulant	Normal	High	High	Thyrotropin-secreting pituitary adenoma, thyroid hormone resistance
Heparin	Anticoagulant	Normal	High	High	Thyrotropin-secreting pituitary adenoma, thyroid hormone resistance
Phenytoin	Antiepileptic agent	Normal	Low	Low end of normal range	Central hypothyroidism
Salsalate	Nonsteroidal anti-inflammatory drug	Normal	Low end of normal range	Low end of normal range	Central hypothyroidism

pendent on exogenous thyroid hormone will have an increased dose requirement after the initiation of oral estrogen treatment, whereas in patients with a functional thyroid, endogenous thyroid hormone production will increase. Transdermal estradiol has minimal effects on thyroxine-binding globulin because this route of administration circumvents the first-pass effect on the liver.[53]

Drug-induced displacement of thyroid hormone from binding proteins occurs with the antiepileptic agents phenytoin and carbamazepine, salsalate and some other nonsteroidal anti-inflammatory drugs, high-dose furosemide, and heparin preparations. The clinical importance of these interactions is often negligible, and in the case of antiepileptic agents and heparin, the effects primarily involve alterations in laboratory testing of thyroid function, discussed below.

DRUGS AFFECTING THYROID HORMONE ACTIVATION, METABOLISM, AND EXCRETION

Conversion of T_4 to T_3 is inhibited by several drugs, including amiodarone, dexamethasone (and other glucocorticoids), propranolol at high doses, the cholecystographic agents ipodate and iopanoic acid (the latter no longer available in the United States), and the antithyroid drug propylthiouracil. Amiodarone inhibits T_3 generation both within the pituitary and in the periphery. Dexamethasone inhibition of T_4-to-T_3 conversion is exploited therapeutically in the treatment of patients with severe thyrotoxicosis.[54] The effect of propranolol on monodeiodination is not clinically relevant at usual doses.

Treatment with drugs that induce glucuronidation enzymes, including phenobarbital, phenytoin, carbamazepine, and rifampin, sometimes necessitates an increase in the dose of levothyroxine.[55,56] Tyrosine kinase inhibitors also appear to augment thyroid hormone metabolism. A study of sorafenib in levothyroxine-dependent patients with thyroid cancer showed that 26 weeks after the start of treatment there was evidence of accelerated levothyroxine inactivation through augmented type 3 deiodinase activity.[57]

Bile acid sequestrants such as cholestyramine, colestipol, and colesevelam reduce thyroid hormone levels in both endogenous and iatrogenic thyrotoxicosis, presumably by interfering with recycling of thyroid hormone in the enterohepatic circulation.[58,59]

DRUGS AFFECTING ABSORPTION OF THYROID HORMONE PREPARATIONS

Thyroid hormone tablets taken orally require an acid milieu for dissolution before being transported to the small bowel for absorption.[60,61] Approximately 60 to 80% of levothyroxine is absorbed within 2 to 4 hours after an oral dose in the fasting state.[61] Daily use of proton-pump inhibitors is associated with an increased levothyroxine requirement[62,63]; this need is met by either increasing the levothyroxine dose or switching to a liquid preparation.[64]

Drugs interfering with gastrointestinal absorp-

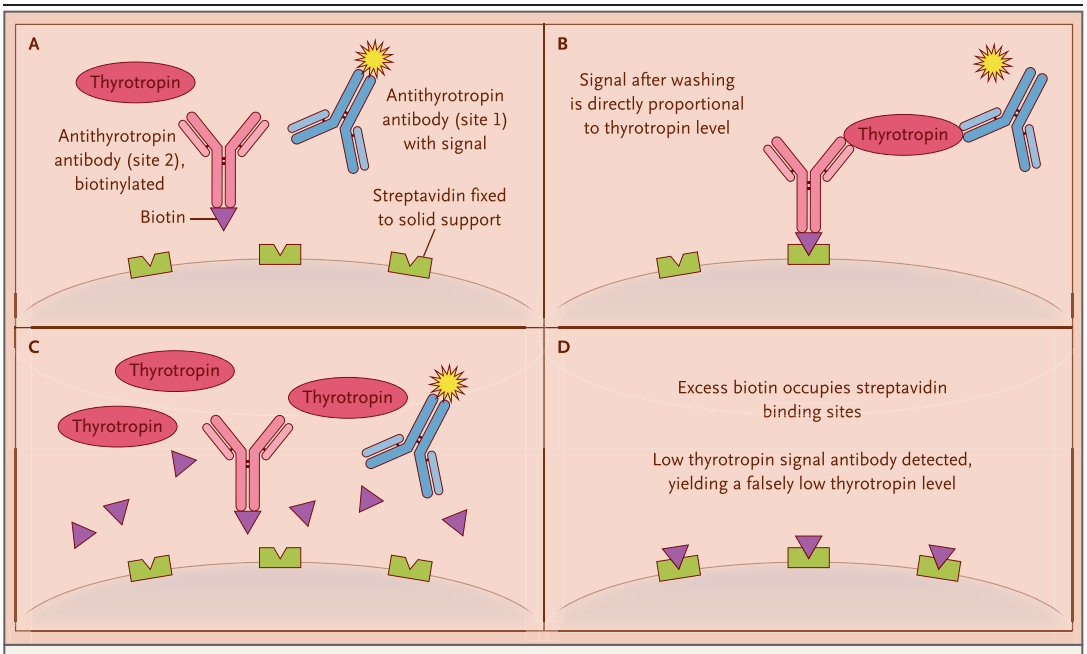


Figure 3. Biotin-Related Interference in Two-Site Thyrotropin Assay Measurements.

Excess biotin results in variable interference in assays using biotinylated reagents. In two-site (sandwich) assays, including those for thyrotropin, the thyrotropin level is falsely low or undetectable. Assay components include a biotinylated antithyrotropin antibody as the capture antibody and a second antithyrotropin antibody to which a signal component has been attached (Panel A). Under normal conditions, the complex consisting of thyrotropin bound to the two antithyrotropin antibodies, one of which is biotinylated, binds to streptavidin, which has been fixed to a solid phase such as an enzyme-linked immunosorbent assay well. After washing, the signal will be directly proportional to the level of thyrotropin in the specimen (Panel B). In the presence of excess biotin (Panel C), the complex of thyrotropin with the antithyrotropin antibodies cannot compete effectively for streptavidin binding on the solid phase. After washing, a low signal results in a falsely low thyrotropin value (Panel D).

tion of thyroid hormone include ferrous sulfate, calcium carbonate, aluminum hydroxide, sucralfate, bile acid sequestrants, and raloxifene. Taking thyroid hormone 4 hours before ingesting any of these medications or moving the levothyroxine dose to bedtime is recommended.[31] An empty stomach is advised, since even soy formula, milk, or coffee can impair absorption.[61] Patients should be informed that starting or stopping these medications will affect the stability of thyroid hormone levels, requiring reassessment after these changes are made.

DRUGS CAUSING ABNORMAL THYROID TESTS IN EUTHYROID PATIENTS

Several drugs are associated with abnormal results of laboratory tests of the thyroid in euthyroid persons (Table 2). Awareness of such interactions and the ability to distinguish these effects from true thyroid dysfunction will prevent unnecessary diagnostic or therapeutic interventions.

BIOTIN

Biotin is used pharmacologically to treat neuromuscular disorders such as multiple sclerosis and is also a popular dietary supplement.[65] In addition, biotinylated laboratory reagents are widely used in clinical laboratories because of their strong noncovalent binding to streptavidin, which is fixed to a solid phase such as magnetic beads or an enzyme-linked immunosorbent assay plate. Commercial assays for free T_4, T_3, thyrotropin, and thyrotropin-receptor antibodies commonly include biotinylation.[66] Numerous reports of biotin-related assay interference leading to incorrect diagnosis and management have been published, including cases in which a falsely low thyrotropin level, a falsely high free T_4 level, and spuriously positive results of thyrotropin-receptor

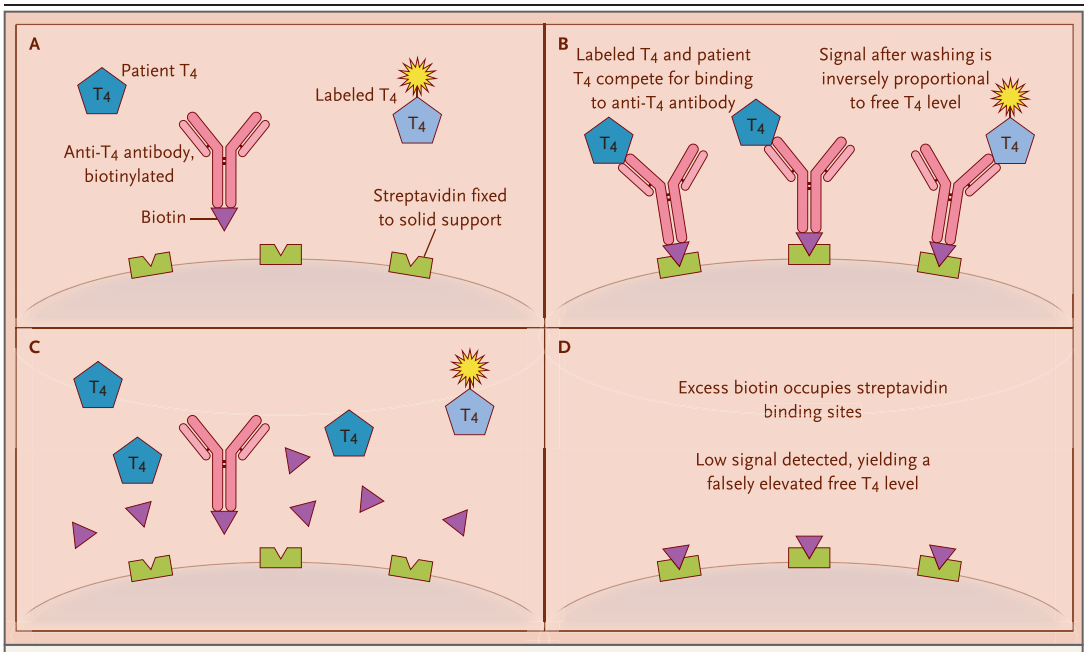


Figure 4. Biotin-Related Interference in Competitive Free T_4 Immunoassays.

In some competitive immunoassays, including those for free T_4, free T_3, and thyrotropin receptor antibodies, the results may be falsely elevated. Free T_4 assay components include labeled T_4 and a biotinylated anti-T_4 antibody, as well as streptavidin bound to a solid phase, such as beads coated with streptavidin (Panel A). Free T_4 in serum from the patient competes with labeled T_4 for binding to the biotinylated anti-T_4 antibody (Panel B). The amount of signal after washing will be inversely proportional to the level of free T_4 in the patient's serum. Excess biotin in the serum monopolizes the streptavidin binding sites, preventing binding of either free T_4–anti-T_4 antibody or labeled T_4–anti-T_4 antibody complexes (Panel C). Since the patient's free T_4 value in the assay is inversely proportional to the amount of label still present after washing, the low or absent signal leads to calculation of a falsely elevated free T_4 value (Panel D).

antibody tests exactly mimicked the biochemical findings of Graves' disease (Figs. 3 and 4).[67] Although such cases often involve biotin doses of 300 mg daily or higher,[68,69] lesser degrees of interference occur with doses as low as 10 mg daily.[70,71] The direction and degree of interference depend on the assay platform; two-site (sandwich) methods, used in most thyrotropin assays, show falsely low values (Fig. 3), and competitive immunoassays for thyroid hormone yield falsely elevated results (Fig. 4).

Given the high prevalence of biotin supplementation in the general population, patients with incongruous results of laboratory tests of the thyroid should be asked whether they take biotin supplements. Assay interference often resolves within 48 hours after discontinuation of biotin,[72] but patients should refrain from using the supplement for several days before testing is repeated.

AMIODARONE

In addition to causing true hypothyroidism and thyrotoxicosis, amiodarone leads to predictable changes in thyroid laboratory test results in euthyroid persons. Inhibition of peripheral and central T_4-to-T_3 conversion by amiodarone and its major active metabolite, desethylamiodarone, leads to reductions in circulating and intrapituitary T_3 levels, thereby stimulating thyrotropin-releasing hormone and thyrotropin release through an absence of negative feedback. Increases in thyrotropin prompt thyroidal release of T_4, which accumulates further because of inhibited conversion to T_3. The net effect of these changes is a serum thyrotropin level that is elevated or at the high end of the normal range, high levels of total and free T_4, and a T_3 level at the low end of the normal range in a euthyroid patient. Elevated T_4 levels in this context can be confused with primary thyrotoxicosis, but an unsuppressed thy-

rotropin level rules out this possibility. Similarly, concurrent elevations of thyrotropin and free T_4 levels can be mistaken for evidence of a thyrotropin-secreting pituitary adenoma or thyroid hormone resistance, but normal values on thyroid testing performed before the initiation of amiodarone therapy, when available, essentially rule out these disorders. Patients with normal thyroid function while receiving levothyroxine therapy may have similar increases in thyrotropin after starting amiodarone.[73]

HEPARIN

Heparin liberates lipoprotein lipase from the vascular endothelium. Blood samples from a patient receiving heparin have increased lipoprotein lipase activity, which persists in vitro. Free thyroid hormone assays with prolonged incubation periods, such as measurement by means of equilibrium dialysis, are most affected, since free fatty acids released by the lipase displace T_4 and T_3 from binding proteins, causing spuriously high values.[74] Similar effects are seen with low-molecular-weight heparin preparations.[75] Standard competitive free hormone assays and thyrotropin testing are generally unaffected, so the testing can be repeated with the use of these assays or the values can be rechecked 24 hours after heparin has been stopped.

PHENYTOIN, CARBAMAZEPINE, AND SALSALATE

In addition to enhancing the metabolism of thyroid hormone, phenytoin and carbamazepine displace T_4 from binding proteins. Although the immediate effect is a transiently elevated free T_4 level with reciprocal thyrotropin suppression, both levels are expected to normalize after an equilibrium is reached. Therefore, it once seemed paradoxical that clinically euthyroid patients taking these medications had low levels of free T_4 and normal thyrotropin levels, suggesting central hypothyroidism. However, it was ultimately determined that reduced free T_4 values in this context are artifactual and are related to serum dilution in assays requiring this step.[76] Similar effects are seen with salsalate.[77]

EFFECT OF THYROID DYSFUNCTION ON DRUG METABOLISM

Both hyperthyroidism and hypothyroidism can affect the pharmacokinetics and efficacy of common drugs, as well as the frequency of adverse effects. Salient examples include warfarin, with a counterintuitive lower dose requirement during hyperthyroidism[78] as a result of accelerated turnover of vitamin K–dependent clotting factors, and statins, which are associated with an increased risk of myopathy in the presence of hypothyroidism.[79,80] Hyperthyroidism accelerates the metabolism of numerous medications, including propranolol, cardiac glycosides, and glucocorticoids,[81] and conversely, hypothyroidism delays clearance of these drugs.

CONCLUSIONS

Drugs interact with the thyroid through diverse mechanisms, disrupting control of the thyroid at the hypothalamic–pituitary level, triggering immune and nonimmune thyroid destruction, inducing or aggravating thyroid autoimmunity, and causing both hypothyroidism and thyrotoxicosis. Drugs affect the binding of thyroid hormone to protein carriers and the conversion of T_4 to T_3, as well as the ultimate metabolism and recycling of thyroid hormone. Numerous drugs affect the efficiency of exogenous thyroid hormone therapy, requiring vigilance to prevent both undertreatment while the drugs are being taken and overtreatment after they have been stopped. Finally, drugs may alter the results of thyroid laboratory tests in a manner that artifactually mimics Graves' disease, central hypothyroidism, and central hyperthyroidism despite the maintenance of a euthyroid state. Awareness of these potential interactions allows clinicians to monitor patients for them, intervene when appropriate, and avoid unnecessary testing and treatment.

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