REVIEW ARTICLE

CURRENT CONCEPTS

Thyroiditis

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The term thyroiditis encompasses many relatively common thyroid disorders, which have been classified according to various schemes (Table 1). In this article we review the diagnosis and treatment of the different types of thyroiditis.

Mechanisms of Autoimmune Thyroid Destruction

Thyroid Autoimmunity

Hashimoto's thyroiditis, painless sporadic thyroiditis, and painless postpartum thyroiditis all have an autoimmune basis (Table 2). In Hashimoto's thyroiditis, the antithyroid immune response begins with activation of thyroid antigen–specific helper T cells. According to one theory, this activation results from infection with a virus that has a protein similar to a thyroid protein, although clear evidence for a viral cause is lacking.[2] According to another theory, thyroid epithelial cells present their own intracellular proteins to T cells. In women, autoimmune thyroiditis may be induced by the accumulation of fetal cells in the maternal thyroid gland during pregnancy (painless postpartum thyroiditis).[3,4]

Once helper T cells are activated, they induce B cells to secrete thyroid antibodies. Increased serum concentrations of thyroid antibodies are present in up to 10 percent of the general population in the United States[5] and in approximately 25 percent of U.S. women over 60 years of age.[6] The prevalence of high serum concentrations of thyroid antibodies varies according to race and ethnic background. In the third U.S. National Health and Nutrition Examination Survey of persons 12 years of age or older, high serum concentrations of thyroid antibodies were present in 14.3 percent of whites, in 10.9 percent of Mexican Americans, and in only 5.3 percent of blacks.[7] The majority of patients with measurable thyroid antibody concentrations have normal thyroid function. In studies in England, 10 percent of postmenopausal women with high serum thyroid antibody concentrations had subclinical hypothyroidism and 0.5 percent had overt hypothyroidism, although euthyroid patients with high serum thyroid antibody concentrations had progression to overt hypothyroidism at a rate of 2 to 4 percent a year.[5,8] In a 10-year prospective study conducted in Switzerland, high serum thyroid peroxidase antibody concentrations predicted the progression of subclinical hypothyroidism to overt hypothyroidism.[9]

The thyroid antibodies most frequently measured are those directed against thyroid peroxidase and against thyroglobulin. The former are closely associated with overt thyroid dysfunction, and their presence tends to correlate with thyroidal damage and lymphocytic inflammation. Thyroid peroxidase antibodies are complement-fixing and thus directly cytotoxic to thyrocytes,[10] but there is limited evidence that this toxic effect is a primary destructive mechanism in autoimmune thyroiditis. Antibodies that block thyrotropin receptors have been reported in up to 10 percent of patients with Hashimoto's

thyroiditis.[11] In some patients, these antibodies may have a role in the development and severity of hypothyroidism, although they are not directly involved in the destruction of thyrocytes. Thyroglobulin antibodies are present less frequently, and their role is unclear. Antibodies to colloid antigen, thyroid hormones, and the sodium iodide symporter have also been detected in patients with autoimmune thyroiditis.

The mechanism for autoimmune destruction of the thyroid probably involves both cellular immunity and humoral immunity. Lymphocytic infiltration of the thyroid gland by equal numbers of B cells and cytotoxic T cells is a common histologic feature of all forms of autoimmune thyroiditis (Fig. 1). In patients with Hashimoto's thyroiditis, thyrocytes express the *Fas* gene, a member of the closely linked group of tumor necrosis factor genes, or supergene family, whereas thyrocytes from normal glands do not. Apoptosis caused by the interaction of the *Fas* gene and the Fas ligand on the surface of thyrocytes may be an underlying cause of thyroid-cell destruction.[12]

GENETIC SUSCEPTIBILITY

The genetics of autoimmune thyroid disease are complex.[13] Association of Hashimoto's thyroiditis and painless postpartum thyroiditis with HLA-DR3, HLA-DR4, and HLA-DR5 has been reported in white persons,[14-16] but other associations have been observed in other racial and ethnic groups. The cytotoxic-T-lymphocyte–associated protein 4 (CTLA-4) gene region may be associated with familial Hashimoto's thyroiditis, although a clear linkage has been difficult to demonstrate. Studies of the association between painless postpartum thyroiditis and the *CTLA-4* gene have been negative.[17] There is a higher incidence of subacute thyroiditis in those with the HLA-Bw35 haplotype.[18]

ENVIRONMENTAL FACTORS

Among patients with Hashimoto's thyroiditis, hypothyroidism is more likely to develop in smokers than in nonsmokers,[19] a finding that may be related to the presence of thiocyanates in cigarette smoke. An increased prevalence of painless postpartum thyroiditis has also been noted among smokers.[20] In addition, geographic variations in the incidence of Hashimoto's thyroiditis, painless postpartum thyroiditis, and painless sporadic thyroiditis suggest that dietary iodine insufficiency may be protective against autoimmune thyroiditis.[21,22]

CLINICAL AND BIOCHEMICAL CHANGES IN THYROIDITIS

The various forms of thyroiditis may cause thyrotoxicosis, hypothyroidism, or both (Fig. 2).

THYROTOXICOSIS

In painless sporadic thyroiditis, painless postpartum thyroiditis, and painful subacute thyroiditis, inflammatory destruction of the thyroid may lead to transient thyrotoxicosis as preformed thyroid hormones are released from the damaged gland. As thyroid hormone stores are depleted, there is often a progression through a period of euthyroidism to hypothyroidism. The first biochemical change in inflammatory thyroiditis before the onset of thyrotoxicosis is an increase in the serum concentration of thyroglobulin.[23] As in other forms of thyrotoxicosis, the serum concentration of thyrotropin is suppressed, and concentrations of total and free triiodothyronine (T_3) and thyroxine (T_4) are elevated. Serum T_4 concentrations are proportionally higher than T_3 concentrations, reflecting the ratio of stored hormone in the thyroid gland (whereas in Graves' disease and in toxic nodular goiter, T_3 is preferentially elevated). The signs and symptoms

Table 1. Terminology for Thyroiditis.

Type	Synonyms
Hashimoto's thyroiditis	Chronic lymphocytic thyroiditis Chronic autoimmune thyroiditis Lymphadenoid goiter
Painless postpartum thyroiditis	Postpartum thyroiditis Subacute lymphocytic thyroiditis
Painless sporadic thyroiditis	Silent sporadic thyroiditis Subacute lymphocytic thyroiditis
Painful subacute thyroiditis	Subacute thyroiditis de Quervain's thyroiditis Giant-cell thyroiditis Subacute granulomatous thyroiditis Pseudogranulomatous thyroiditis
Suppurative thyroiditis	Infectious thyroiditis Acute suppurative thyroiditis Pyrogenic thyroiditis Bacterial thyroiditis
Drug-induced thyroiditis (amiodarone, lithium, interferon alfa, interleukin-2)	
Riedel's thyroiditis	Fibrous thyroiditis

Table 2. Characteristics of Thyroiditis Syndromes.*

Characteristic	Hashimoto's Thyroiditis	Painless Postpartum Thyroiditis	Painless Sporadic Thyroiditis	Painful Subacute Thyroiditis	Suppurative Thyroiditis	Riedel's Thyroiditis
Age at onset (yr)	All ages, peak 30–50	Childbearing age	All ages, peak 30–40	20–60	Children, 20–40	30–60
Sex ratio (F:M)	8–9:1	—	2:1	5:1	1:1	3–4:1
Cause	Autoimmune	Autoimmune	Autoimmune	Unknown	Infectious	Unknown
Pathological findings	Lymphocytic infiltration, germinal centers, fibrosis	Lymphocytic infiltration	Lymphocytic infiltration	Giant cells, granulomas	Abscess formation	Dense fibrosis
Thyroid function	Hypothyroidism	Thyrotoxicosis, hypothyroidism, or both	Thyrotoxicosis, hypothyroidism, or both	Thyrotoxicosis, hypothyroidism, or both	Usually euthyroidism	Usually euthyroidism
TPO antibodies	High titer, persistent	High titer, persistent	High titer, persistent	Low titer, or absent, transient	Absent	Usually present
ESR	Normal	Normal	Normal	High	High	Normal
24-Hour ^{123}I uptake	Variable	<5%	<5%	<5%	Normal	Low or normal

* Information is from Farwell and Braverman.[1] TPO denotes thyroid peroxidase, ESR erythrocyte sedimentation rate, and ^{123}I iodine-123.

of thyrotoxicosis due to thyroiditis are usually not severe.

HYPOTHYROIDISM

The hypothyroid phase of thyroiditis results from the gradual depletion of stored thyroid hormones. Although chronic hypothyroidism is most closely associated with Hashimoto's thyroiditis, all types of thyroiditis may progress to permanent hypothyroidism. This outcome is more likely in patients with higher serum concentrations of thyroid antibodies or in patients in whom a more severe hypothyroid phase develops. As thyroid function diminishes, serum thyrotropin concentrations rise. The combination of elevated serum thyrotropin concentrations and normal free T_4 and T_3 concentrations is termed "subclinical hypothyroidism," or "mild thyroid failure."[24] As thyroid failure progresses, serum T_4 concentrations fall, and the combination of elevated thyrotropin concentrations and low T_4 concentrations is termed "overt hypothyroidism." Serum total and free T_3 concentrations may not fall until the disease is far advanced, because increased serum thyrotropin concentrations stimulate the thyroid to release T_3. In most patients, once the serum T_3 concentrations fall below the normal level, the classic symptoms and signs of hypothyroidism appear.

TYPES OF THYROIDITIS

HASHIMOTO'S THYROIDITIS

Hashimoto's thyroiditis (Fig. 1A), which is characterized by the presence of high serum thyroid antibody concentrations and goiter, is the most common type of thyroiditis. In the United States and other countries where the ordinary diet provides sufficient iodine (median urinary iodine levels, >100 μg per liter), Hashimoto's thyroiditis is the most frequent cause of hypothyroidism and goiter. In an occasional patient, hyperthyroidism alternates with hypothyroidism, most likely owing to the intermittent presence of thyroid-stimulating and thyroid-blocking antibodies.[25]

A firm, bumpy, symmetric, painless goiter is frequently the initial finding in Hashimoto's thyroiditis. About 10 percent of patients with chronic autoimmune hypothyroidism have atrophic thyroid glands (rather than goiter), which may represent the final stage of thyroid failure in Hashimoto's thyroiditis.[26] High serum thyroid peroxidase antibody concentrations are present in 90 percent of patients with Hashimoto's thyroiditis, and high serum thyroglobulin antibody concentrations are present in 20 to 50 percent of these patients.[27] The thyroid appears hypoechogenic on ultrasound examination.

The 24-hour radioactive iodine (iodine-123 [^{123}I]) uptake is not helpful in establishing the diagnosis.

Once overt hypothyroidism is present, levothyroxine sodium is the treatment of choice for Hashimoto's thyroiditis. We also use levothyroxine sodium to treat patients with subclinical hypothyroidism and high serum thyroid antibody concentrations, because the progression to overt hypothyroidism is common[9] and because hyperlipidemia and atherosclerotic heart disease may develop in patients with subclinical hypothyroidism.[28,29] The goal of replacement therapy with levothyroxine sodium is normalization of serum thyrotropin values.

In patients with Hashimoto's thyroiditis and a large goiter, thyrotropin-suppressing doses of levothyroxine sodium can be given over the short term (i.e., six months) to decrease the size of the goiter. In most patients with Hashimoto's thyroiditis (whether their condition is euthyroid or hypothyroid), goiter size will decrease by 30 percent after six months of therapy with levothyroxine sodium.[30] Replacement doses should be resumed if the size of the goiter does not decrease. Because serum thyroid antibody concentrations do not decrease with levothyroxine sodium therapy,[31,32] except in some patients with hypothyroidism,[33] monitoring of these concentrations is not indicated once the diagnosis of Hashimoto's thyroiditis has been made.

Although thyroid lymphoma is very rare, the risk of this disease is increased by a factor of 67 in patients with Hashimoto's thyroiditis.[34] Patients with Hashimoto's thyroiditis and a dominant thyroid nodule should undergo fine-needle aspiration biopsy to rule out lymphoma and thyroid carcinoma. When thyroid carcinoma occurs in patients with this type of thyroiditis or other lymphocytic infiltration, the prognosis appears to be more favorable than when it does not.[35]

PAINLESS POSTPARTUM THYROIDITIS

Painless postpartum thyroiditis (Fig. 1B) causes lymphocytic inflammation of the thyroid within the first few months after delivery. It occurs in up to 10 percent of women in the United States, although estimates vary.[36,37] The disease is most common in women who have high serum thyroid peroxidase antibody concentrations during the first trimester of pregnancy or immediately after delivery and in those with other autoimmune disorders, such as type 1 diabetes mellitus, or with a family history of autoimmune thyroid disease.

In only one third of patients with painless post-

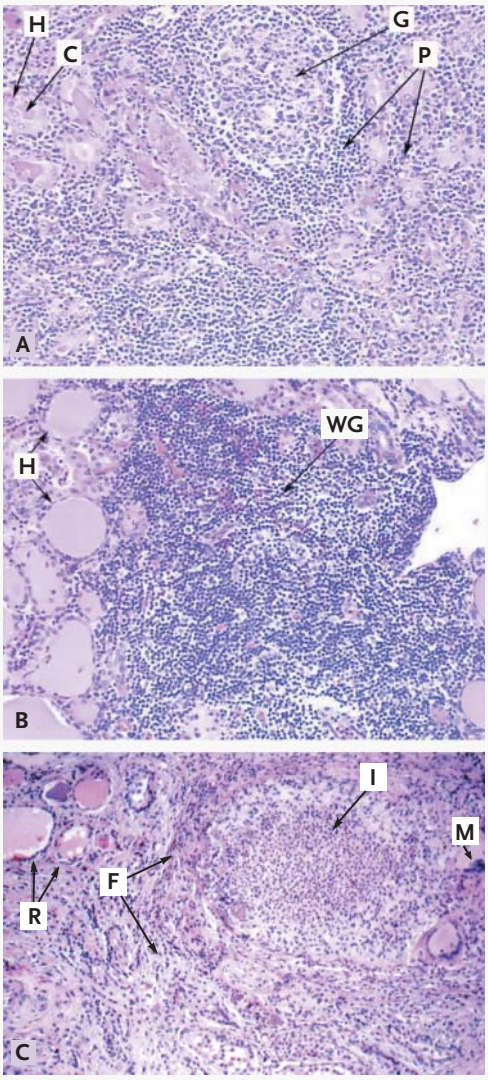

Figure 1. Specimens from Patients with Hashimoto's Thyroiditis (Panel A), Painless Postpartum Thyroiditis (Panel B), and Painful Subacute Thyroiditis (Panel C) (Hematoxylin and Eosin, ×200).

The specimen in Panel A shows typical changes of Hashimoto's thyroiditis, including lymphoid follicles with germinal centers (G), small lymphocytes and plasma cells (P), thyroid follicles with Hürthle-cell metaplasia (H), and minimal colloid material (C). The specimen in Panel B, obtained from a patient with painless postpartum thyroiditis, shows normal follicles with minimal Hürthle-cell metaplasia (H) and dense lymphocytic infiltration (WG) without germinal centers. The specimen in Panel C, obtained from a patient with painful subacute thyroiditis, shows characteristic residual follicles (R), fibrotic bands (F), mixed inflammation (I), and a multinucleated giant cell (M).

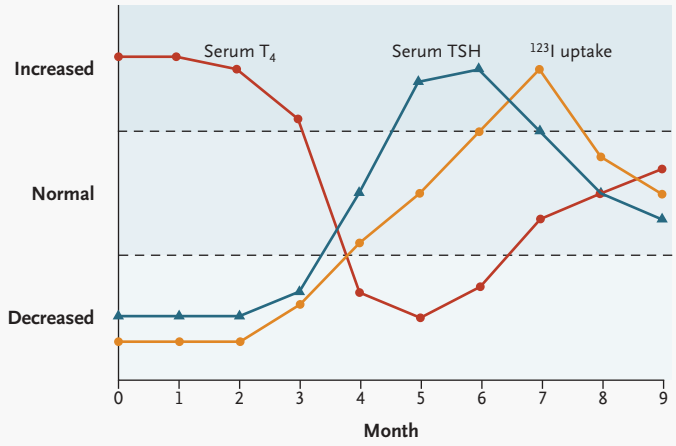

Figure 2. Clinical Course of Painful Subacute Thyroiditis, Painless Postpartum Thyroiditis, and Painless Sporadic Thyroiditis.

Measurements of serum thyrotropin (TSH) and iodine-123 (^{123}I) uptake show thyrotoxicosis during the first three months, followed by hypothyroidism for three months and then by euthyroidism. T_4 denotes thyroxine.

partum thyroiditis will the classic triphasic thyroid hormone pattern develop (Fig. 2). Thyrotoxicosis typically begins one to six months after delivery and lasts for one to two months. That phase may be followed by a hypothyroid phase starting four to eight months after delivery and lasting four to six months. Eighty percent of women recover normal thyroid function within a year; in one follow-up study, however, permanent hypothyroidism developed within seven years in 50 percent of the women studied.[38] Chronic hypothyroidism is more likely in multiparous women or in those with a history of spontaneous abortion.[39] After a first episode of painless postpartum thyroiditis, there is a 70 percent chance of recurrence with subsequent pregnancies.[40]

In most cases of painless postpartum thyroiditis, a small, nontender, firm goiter is present. High serum concentrations of thyroid peroxidase antibodies, thyroglobulin antibodies, or both, are also present.[41] The erythrocyte sedimentation rate is normal. The 24-hour ^{123}I uptake may be used to distinguish painless postpartum thyroiditis from postpartum Graves' disease; the uptake is low (<5 percent) in women with painless postpartum thyroiditis, whereas it is elevated in those with Graves' disease. This test should be performed in patients with symptomatic thyrotoxicosis when there are no clear signs of Graves' disease, such as large goiter or ophthalmopathy. Because radioactive iodine is secreted in breast milk and ^{123}I has a half-life of 13 hours, nursing mothers need to pump and discard milk for at least two days after the test.

Mild thyrotoxicosis rarely requires therapy, but when the disease is severe, it is treated with beta-blockers. Antithyroid drug therapy is contraindicated, because there is no excess thyroid hormone production. Treatment of the hypothyroid phase may not be necessary, but if this phase is prolonged or if the patient is symptomatic, levothyroxine sodium should be given, then withdrawn after six to nine months to determine whether thyroid function has normalized.

PAINLESS SPORADIC THYROIDITIS

Painless postpartum thyroiditis and painless sporadic thyroiditis are indistinguishable except by the relation of the former to pregnancy.[42] The latter disease is more difficult to study because of its sporadic nature. These syndromes may represent a subacute form of Hashimoto's thyroiditis. Painless sporadic thyroiditis[43] may account for about 1 percent of all cases of thyrotoxicosis. The clinical course is similar to that of painless postpartum thyroiditis. Although abnormalities in thyroid function resolve in most patients, 20 percent of patients will have residual chronic hypothyroidism.[44] Symptoms are usually mild. A small, nontender, very firm, diffuse goiter is present in 50 percent of these patients.[45] High serum thyroid peroxidase antibody concentrations are present in 50 percent of patients at the time of diagnosis, with lower titers, on average, than in Hashimoto's thyroiditis.[45] A low or undetectable concentration of ^{123}I at 24 hours can be diagnostic, and the test should be performed when the cause of the thyrotoxicosis is unclear, in order to avoid inappropriate treatment with antithyroid drugs. Therapy is the same as that for painless postpartum thyroiditis. Overall recurrence rates have not been well established.

PAINFUL SUBACUTE THYROIDITIS

Painful subacute thyroiditis (Fig. 1C), which is a self-limited inflammatory disorder, is the most common cause of thyroid pain. It occurs in up to 5 percent of patients with clinical thyroid disease.[46] It frequently follows an upper respiratory tract infection, and its incidence is highest in summer, correlating with the peak incidence of enterovirus.[47] A viral cause of subacute thyroiditis has therefore been proposed,[48] but so far clear evidence for it is lacking.

Subacute thyroiditis begins with a prodrome of

generalized myalgias, pharyngitis, low-grade fever, and fatigue. Patients then present with fever and severe neck pain, swelling, or both. Up to 50 percent of patients have symptoms of thyrotoxicosis. In most patients, thyroid function will be normal after several weeks of thyrotoxicosis, and hypothyroidism will subsequently develop, lasting four to six months, as in painless sporadic thyroiditis and painless postpartum thyroiditis. Although thyroid function normalizes spontaneously in 95 percent of patients over a period of 6 to 12 months, residual hypothyroidism persists in 5 percent of patients.[1,49] Painful subacute thyroiditis recurs in only about 2 percent of patients.[50]

The hallmark of painful subacute thyroiditis is a markedly elevated erythrocyte sedimentation rate. The C-reactive protein concentration is similarly elevated.[51] The leukocyte count is normal or slightly elevated. Peripheral-blood thyroid hormone concentrations are elevated, with ratios of T_4 to T_3 of less than 20, reflecting the proportions of stored hormone within the thyroid,[52] and serum concentrations of thyrotropin are low or undetectable. Serum thyroid peroxidase antibody concentrations are usually normal. The 24-hour ^{123}I uptake is low (<5 percent) in the toxic phase of subacute thyroiditis, distinguishing this disease from Graves' disease. Color-flow Doppler ultrasonography may also help to make this distinction; in patients with Graves' disease the thyroid gland is hypervascular, whereas in patients with painful subacute thyroiditis the gland is hypoechogenic and has low-to-normal vascularity.[53]

The treatment for painful subacute thyroiditis is to provide symptomatic relief only. Nonsteroidal medications or salicylates are adequate to control mild thyroid pain. For more severe thyroid pain, high doses of glucocorticoids (e.g., 40 mg of prednisone daily) provide immediate relief; doses should be tapered over a period of four to six weeks. Corticosteroids should be discontinued when the ^{123}I uptake returns to normal. Beta-blockade controls the symptoms of thyrotoxicosis. Therapy with levothyroxine sodium is rarely required, because the hypothyroid phase is generally mild and transient, but it is indicated for symptomatic patients.

SUPPURATIVE THYROIDITIS

Suppurative thyroiditis is usually caused by bacterial infection, but fungal, mycobacterial, or parasitic infections may also occur as the cause. The thyroid is resistant to infection, because of its encapsulation, high iodide content, rich blood supply, and extensive lymphatic drainage, and suppurative thyroiditis is therefore rare.[54] It is most likely to occur in patients with preexisting thyroid disease (thyroid cancer, Hashimoto's thyroiditis, or multinodular goiter), those with congenital anomalies such as a pyriform sinus fistula (the most common source of infection in children), and those who are immunosuppressed, elderly, or debilitated; it is particularly likely to occur in patients with the acquired immunodeficiency syndrome (AIDS), in whom *Pneumocystis carinii* and other opportunistic thyroid infections have been reported.[55,56]

Patients with suppurative bacterial thyroiditis are usually acutely ill with fever, dysphagia, dysphonia, anterior neck pain and erythema, and a tender thyroid mass. Symptoms may be preceded by an acute upper respiratory infection. The presentation of fungal infection, parasitic infection, mycobacterial thyroiditis, and opportunistic thyroid infection in patients with AIDS tends to be chronic and insidious.

Thyroid function is generally normal in patients with suppurative thyroiditis, but both thyrotoxicosis and hypothyroidism have been reported.[54] Leukocyte counts and erythrocyte sedimentation rates are elevated. Suppurative areas appear "cold" on radioactive-iodine scanning. Fine-needle aspiration biopsy with Gram's staining and culture is the diagnostic test of choice. The therapy for suppurative thyroiditis consists of appropriate antibiotics and drainage of any abscess. The disease may prove fatal if diagnosis and treatment are delayed.

DRUG-INDUCED THYROIDITIS

Many medications can alter thyroid function or the results of thyroid-function tests. However, only a few are known to provoke autoimmune or destructive inflammatory thyroiditis.

Amiodarone

The various effects of amiodarone on the thyroid (Table 3) and the peripheral metabolism of the thyroid hormones have recently been reviewed.[57] Amiodarone-induced hypothyroidism, which is due to excess iodine, occurs in up to 20 percent of patients in iodine-sufficient regions. Patients with preexisting thyroid autoimmunity are at increased risk for the development of hypothyroidism while receiving amiodarone. Treatment with levothyroxine sodium is indicated in hypothyroid patients, and amiodarone may be continued. The dose of levothyroxine

Table 3. Features of Amiodarone-Induced Thyroid Dysfunction.

Feature	Type I Thyrotoxicosis	Type II Thyrotoxicosis	Hypothyroidism
Mechanism	Excess iodine (common in iodine-deficient areas)	Destructive inflammatory thyroiditis	Excess iodine (common in iodine-sufficient areas)
Thyroid antibodies	Often present	Usually absent	Often present
Thyroid function	Thyrotoxicosis	Thyrotoxicosis	Hypothyroidism
24-Hour ^{123}I uptake*	Low in iodine-sufficient regions but may be normal or increased in iodine-deficient areas	<5%	Usually low in iodine-sufficient regions
Findings on color Doppler ultrasonography	Hypervascularity	Reduced blood flow	Variable
Therapy	High-doses of antithyroid drugs — possibly potassium perchlorate, or iopanoic acid before thyroidectomy	High doses of corticosteroids, iopanoic acid	Levothyroxine sodium

* ^{123}I denotes iodine-123.

sodium needed to normalize the serum concentration of thyrotropin is often higher than the usual dose, because amiodarone decreases 5′-deiodinase activity in peripheral tissues, thus also decreasing production of T_3.

Amiodarone-induced thyrotoxicosis occurs in up to 23 percent of patients receiving amiodarone and is far more prevalent in iodine-deficient regions.[58] Type I amiodarone-induced thyrotoxicosis is defined as synthesis and release of excessive thyroid hormone; it is iodine-induced, and it is more likely to occur in patients with preexisting subclinical thyroid disorders, especially nodular goiter. Type II amiodarone-induced thyrotoxicosis is a destructive thyroiditis that causes the release of preformed thyroid hormone from the damaged thyroid gland. Distinguishing between the two forms of amiodarone-induced thyrotoxicosis is difficult, especially since some patients have both types. In patients in the United States, ^{123}I uptake values are typically low in type I and type II amiodarone-induced thyrotoxicosis. Color-flow Doppler ultrasonography may show hypervascularity in type I disease but reduced blood flow in type II.[59] Although the serum interleukin-6 concentration was initially reported to be more elevated in type II amiodarone-induced thyrotoxicosis than in type I,[60] subsequent studies have not replicated this finding.

Type I amiodarone-induced thyrotoxicosis is best treated with high doses of antithyroid drugs (methimazole or propylthiouracil), sometimes with the addition of potassium perchlorate to prevent further uptake of iodine by the thyroid. Lithium has also been suggested as therapy for type I disease.[61] Type II amiodarone-induced thyrotoxicosis responds to high-dose corticosteroids. Iopanoic acid has recently been reported to be effective in patients with type II amiodarone-induced thyrotoxicosis,[62] although less so than corticosteroids,[63] and in those with type I disease who require thyroidectomy.[64]

Careful examination of the thyroid, base-line thyroid-function tests, and measurements of serum concentrations of thyroid peroxidase and thyroglobulin antibodies should be performed before amiodarone therapy is instituted, and thyroid function should be monitored every six months as long as patients are receiving the drug (Fig. 3).

Lithium

In patients with preexisting thyroid autoimmunity, lithium may increase the serum thyroid antibody concentrations and lead to subclinical or overt hypothyroidism.[65] Estimates of the prevalence of high serum thyroid antibody concentrations in patients receiving long-term treatment with lithium range from 10 to 33 percent.[66] In addition, thyrotoxicosis has been reported after long-term lithium use,[67] possibly caused by lithium's direct toxic effects on thyroid cells or by lithium-induced painless sporadic thyroiditis.[68,69]

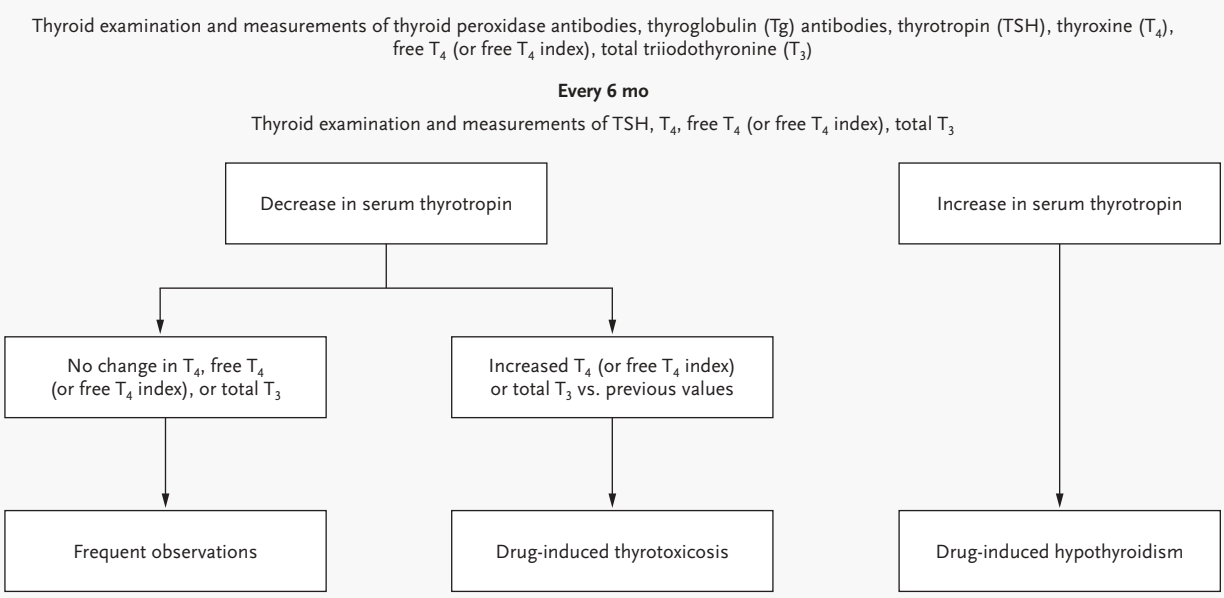

Figure 3. Monitoring Thyroid Function in Patients Receiving Amiodarone Therapy.
Adapted from Martino et al.,[57] with the permission of the publisher.

Interferon Alfa and Interleukin-2

In up to 15 percent of patients without previous thyroid autoimmunity, high serum thyroid peroxidase antibody concentrations or thyroid dysfunction will develop during interferon alfa therapy.[70] High serum thyroid peroxidase antibody concentrations in such patients and in patients receiving interleukin-2 therapy may be associated with overt or subclinical hyperthyroidism (Graves' disease) or hypothyroidism.[71] Interferon alfa has also been reported to cause destructive inflammatory thyroiditis.[72,73] The measurement of ^{123}I uptake helps to distinguish between drug-induced Graves' disease, in which the uptake is elevated, and drug-induced inflammatory thyroiditis, in which the uptake is low, in patients with thyrotoxicosis.

When Graves' disease develops in patients receiving interferon alfa therapy, they should be treated with antithyroid drugs. While treatment with interferon alfa or interleukin-2 is continued, the thyrotoxic phase of inflammatory thyroiditis can be treated with beta-blockers and, if necessary, with nonsteroidal antiinflammatory drugs or corticosteroids, and the hypothyroidism can be treated with levothyroxine sodium. Although thyroid function usually normalizes when cytokine therapy is discontinued, affected patients are at increased risk for autoimmune thyroid dysfunction in the future. Thyroid-function tests and measurements of serum thyroid antibodies should be performed before therapy with interferon alfa or interleukin-2 is initiated and every six months thereafter.

RIEDEL'S THYROIDITIS

Riedel's thyroiditis, a local manifestation of a systemic fibrotic process,[74] is a progressive fibrosis of the thyroid gland that may extend to surrounding tissues. The prevalence of this disease is only 0.05 percent among patients with thyroid disease requiring surgery, and its cause is unknown. High serum thyroid antibody concentrations are present in up to 67 percent of patients, but it is unclear whether the antibodies are a cause or effect of the fibrotic thyroid destruction.

Patients with Riedel's thyroiditis present with a rock-hard, fixed, painless goiter. They may have symptoms due to tracheal or esophageal compression or hypoparathyroidism due to extension of the fibrosis into adjacent parathyroid tissue. Most patients are euthyroid at presentation but become hypothyroid once replacement of normal thyroid tissue is nearly complete. A definitive diagnosis is

made by open biopsy. The treatment is surgical, although therapy with glucocorticoids, methotrexate, and tamoxifen has been reported to be successful in the early stages of the disease.[75,76]

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