Hyperthyroidism and Thyrotoxicosis

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Introduction

The term thyrotoxicosis applies to a clinical condition resulting from increased thyroid hormone concentration and action. When the clinical condition is diagnosed by appropriate laboratory tests, the etiology should be determined. A high radioiodine uptake of thyroid will usually indicate either a very common condition called Graves' hyperthyroidism or a very uncommon TSH-secreting pituitary adenoma. A very low uptake or no uptake will indicate destructive thyroiditis, iodine-induced hyperthyroidism, or very rare cases of extra-thyroidal thyroid hormone production or exogenous thyroid hormone intake. Normal radioactive thyroid uptake can occur in mild Graves' hyperthyroidism or in multinodular toxic goiter and toxic adenoma. Management should be problem oriented and should depend on the etiology. Antithyroid medications, surgery, or radioactive iodine therapy can be used for high uptake types, and symptomatic therapy can be used for destructive thyroiditis. Iodine-induced hyperthyroidism will respond to antithyroid medications and elimination of exogenous iodine.

When the etiology is related to increased rate of thyroid hormone synthesis, the term hyperthyroidism is applicable. Thyrotoxicosis can also result from a destructive process in the thyroid resulting in unregulated excess release of stored thyroid hormones without increased production [1, 2]. The thyrotoxicosis syndrome may also be due to exogenous source either iatrogenic or factitious. Hyperthyroidism is considered subclinical if TSH is low with normal FT4 and FreeT3. In this case hypothalamus–pituitary axis senses the excess, and the negative feedback mechanism results in suppressed or abnormally low thyrotrophic hormone (TSH). Thus it can be argued that this is a biochemical definition rather than a clinical one. Subclinical hyperthyroidism may

be symptomatic or asymptomatic but in either case could have adverse effects [3]. In the United States, subclinical hyperthyroidism is more common (0.7%) than clinical hyperthyroidism (0.5%), however much less common than subclinical hypothyroidism (3–10%). If biologic activity of thyroid hormones is reduced such as in thyroid hormone resistance [4], increased peripheral thyroid levels do not result in thyrotoxicosis syndrome.

Thyrotoxicosis is a syndrome with many diverse etiologies [1]. When clinical symptomatology along with biochemical findings establishes excess thyroid hormone effect, diagnostic measures should be directed at finding the specific etiology, since management and therapy will depend on the etiology. Graves' hyperthyroidism is the most common cause of hyperthyroidism in the United States. Toxic multinodular goiter and toxic adenomas are the next common causes. Nodular toxic goiter is more common in older individuals and in geographic areas with historical iodine deficiency [5]. Inappropriate excess thyroxine (T4) therapy or T4 suppressive therapies for follicular cell-derived thyroid cancer are also common causes of subclinical hyperthyroidism.

The first step after establishing the diagnosis of thyrotoxicosis syndrome, if not contraindicated because of pregnancy or lactation, is to obtain a radioactive iodine uptake of thyroid. High radioactive iodine uptake (RAIU) in iodine-sufficient areas is consistent with Graves' hyperthyroidism and very rarely TSH-producing pituitary adenoma or trophoblastic disease. Occasionally toxic nodular goiter may have mildly elevated uptake, but usually uptake is normal and sometimes low [6]. In Graves' disease degree of elevated uptake is usually proportional to the severity of Graves' disease; subclinical cases may have normal uptake. Very low and near-zero RAIU is consistent with silent thyroiditis, subacute thyroiditis, postpartum thyroiditis, iodine-induced hyperthyroidism, drug-induced hyperthyroidism, or any cause of hyperthyroidism after iodine contrast studies or excess exogenous iodine consumption. Normal RAI uptake can be associated with mild or subclinical hyperthyroidism of Graves' disease or nodular toxic goiter.

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Hyperthyroidism associated with Graves' disease is an autoimmune condition in which the pathogenesis of hyperthyroidism is stimulation of TSH receptors by TSH receptor antibodies (TRAB) [7]. Pathogenesis of extra-thyroidal manifestations such as ophthalmopathy and dermopathy is less clear. Interaction of TRAB with TSH receptors in non-thyroidal tissues is important in the pathogenic process [7, 8].

Recently published 2016 American Thyroid Association (ATA) guidelines for the management of various types of thyrotoxicosis conditions are an excellent source since recommendations are problem oriented [2].

Presentation of Thyrotoxicosis State

Thyrotoxicosis usually presents with weight loss despite an increased appetite. Common symptoms are also palpitations, decreased exercise tolerance and dyspnea, nervousness, heat intolerance and excessive sweating, tremor, irritability, sleep disorder, and muscle weakness of varying degrees. In older individuals hyper-stimulation and adrenergic symptoms are less marked, and patients may be apathetic and complain of fatigue, weight loss, and muscle weakness, or the disease may present with cardiac findings such as atrial fibrillation or heart failure. Increased appetite may be absent in the older patients who often have anorexia. In younger patients occasionally increased appetite may prevent weight loss, and in a few cases, even weight gain is reported [9]. Pedal edema can be present without heart failure because of vasodilation. Gynecomastia may be present in severe cases. Diarrhea is a feature but most patients may have only more frequent bowel movements. In the case of Graves' disease, an enlarged firm thyroid may be present, but some patients have normal size thyroid. In Graves' disease continuous bruits over thyroid may be audible, and flow murmur of carotid or venous hum may also be present [10]. Onset of symptoms in Graves' disease is subacute over weeks, or months, whereas in multinodular toxic goiter, it is slow and subtle over a longer period of time [10]. In the latter a palpable nodular goiter is present or may become visible after weight loss. Graves' disease may present with extra-thyroidal manifestations such as ophthalmopathy and dermopathy. Thyrotoxicosis may precede extra-thyroidal manifestations, occur simultaneously, or in some cases may develop later [7, 11]. Mild stare of the eyes may be present in severely thyrotoxic patients who do not have ophthalmopathy but is not a prominent sign in my experience. Thyroid dermapothy in Graves' disease is usually a later manifestation and is associated with ophthalmopathy and high level of autoimmunity [12].

Clinical Presentations of Thyrotoxicosis Mimicking Other Conditions

Severe proximal muscle weakness in individuals older than age 50 may result in neurology referral before diagnosis is made. Also, in the same age group, atrial fibrillation or congestive heart failure may result in cardiology consultation. Symptoms of thyrotoxicosis are similar to anxiety disorder, and diagnosis is missed if thyroid dysfunction is not considered. In cases of postpartum thyroiditis 2–3 months after childbirth, symptoms in the mother can be attributed to poor sleep and newborn care, and thyroid diagnosis is often overlooked. Elderly patients commonly present with apathetic form and do not have the usual hyper-stimulated features. Thus diagnosis may be missed and malignancy or depression may be suspected. In patients presenting with diarrhea and weight loss, malabsorption or gastrointestinal conditions will be in the differential diagnosis. Some patients may have hypercalcemia, and differential diagnosis of hypercalcemia initially may be a consideration before correct diagnosis [6, 10].

Laboratory studies may also be misleading. Suppressed TSH can be seen in pituitary problems, in euthyroid sick syndrome, and with medications such as high-dose corticosteroids. Elevated peripheral thyroid hormone levels can be seen in thyroid hormone resistance. In cases with increased thyroxine binding capacity, if only total T3 and T4 levels are measured, T4 and T3 levels will be high, but TSH will be normal [10].

A hypokalemic periodic paralysis syndrome can occur with thyrotoxicosis [13]. It is more common in Asian patients and much less common in other ethnic groups [14]. A genetic predisposition is needed, and attacks of paralysis are precipitated by high carbohydrate intake and exercise. Acute attacks should be treated with parenteral potassium administration. Management of hyperthyroidism should be urgent and definitive for achievement of euthyroidism by RAI or surgery [13]. To achieve immediate euthyroidism, surgical thyroidectomy may be the best management in some cases of thyrotoxic hypokalemic periodic paralysis.

Thyrotoxicosis Syndromes (Table 1.1)

Hyperthyroidism Associated with High Thyroid RAIU [5]

These conditions include Graves' disease, TSH-secreting pituitary adenoma, and trophoblastic disease because of stimulation of thyroid by HCG, TSH receptor-activating mutations, and hyperthyroidism in pituitary thyroid hormone resistance and occasional cases of nodular goiter.

Table 1.1 Causes of thyrotoxicosis

Hyperthyroidism associated with elevated or normal thyroid radioactive iodine uptake
Graves' hyperthyroidism[a]
Multinodular goiter or toxic adenoma
TSH-producing pituitary adenoma[b]
Some cases of thyroid hormone resistance
Hyperthyroidism associated with trophoblastic disease
TSH receptor-activating mutations
Hyperthyroidism in some cases of McCune–Albright syndrome

[a]In mild cases RAI uptake may be normal
[b]Usually uptake is normal or occasionally low

Table 1.2 Causes of thyrotoxicosis

Thyrotoxicosis associated with near-zero thyroid radioactive iodine uptake
Silent thyroiditis
Postpartum thyroiditis
Surgery induced manipulation for non-thyroid neck surgery such as neck malignancy or parathyroid surgery
Granulomatous (subacute thyroiditis or de Quervain's)
Acute infectious thyroiditis
External beam radiation-induced thyroiditis
Extensive metastatic follicular cancer encountered after thyroidectomy
Iatrogenic or factitious
Struma ovarii
Bleeding into functioning thyroid nodule
Amiodarone-induced thyroiditis
Drug-induced and biotherapy-induced thyroiditis
Thyrotoxicosis from meat or sausage with high thyroid tissue contamination
Iodine-induced hyperthyroidism
Any hyperthyroid cause associated with exogenous iodine ingestion or iodinated radiologic contrast (depending on the cause uptake may be low but not near zero)

Hyperthyroidism Associated with Normal RAIU

In all of the above conditions of mild degree, in particular if hyperthyroidism is subclinical, radioiodine thyroid uptake may be normal [5]. RAI uptake is usually normal in toxic multinodular goiter and toxic adenoma. Some cases of multinodular goiter may have low radioactive iodine uptake [6].

Thyrotoxicosis Associated with Very Low or Near-Zero (Table 1.2) Neck RAIU [2, 5]

These include iodine-induced hyperthyroidism, silent thyroiditis, granulomatous thyroiditis [15, 16], postpartum thyroiditis [17], and any form of thyrotoxicosis associated with exogenous iodine. One rare cause is struma ovarii [18] when thyroid RAIU is very low and pelvic ultrasound followed by pelvic radioactive iodine scan will be diagnostic. Silent and postpartum thyroiditis has a similar course as subacute gran-

Table 1.3 Medications commonly used in management of thyrotoxicosis

Symptomatic therapy		
Short-acting propranolol[a]	10–40 mg	TID–QID
Slow-release propranolol	70–240 mg	QD–BID
Atenolol[b]	25–100 mg	QD–BID
Nadolol[c]	40–160 mg	QD
Antithyroid medications		
Methimazole, starting dose[d]	10–40 mg/day	QD–BID
Methimazole, maintenance dose	5–20 mg/day	QD
Propylthiouracil (PTU), starting dose[e]	100–400 mg/day	TID
Propylthiouracil (PTU), maintenance dose Saturated solution of potassium iodide[f] 5 drops (0.25 cc or 250 mg) BID alternative is lugol solution	50–200 mg/day	BID–TID

[a]Propranolol is a nonselective beta-blocker and has the potential of reducing T4 to T3 conversion at high doses. It is contraindicated in asthma. Should be stopped when thyroxine levels normalize
[b]Atenolol is a selective beta-1 adrenergic blocker
[c]Nadolol is a nonselective beta-blocker and also has possibility of inhibiting T4–T3 conversion
[d]Methimazole has lower side effect profile than PTU and can be given once a day. It is the drug of choice except for first trimester of pregnancy
[e]PTU has higher rate of hepatic side effects and has to be given divided. Is the only antithyroid used in first trimester of pregnancy
[f]Potassium iodide is mostly used for preoperative preparation of Graves' disease or management of thyroid storm. Although it has been reported for chronic use, ATA has no recommendations for or against its chronic use for therapy of mild Graves' hyperthyroidism [2]

ulomatous thyroiditis, but pain is not present and etiologies are either autoimmune [17] or drugs. Sedimentation rate will be normal and antithyroid antibodies will be positive. Palpation and surgical manipulation of thyroid may also cause transient thyrotoxicosis [19]. For diagnosis of silent thyroiditis, absence of history of iodine intake and iodinated contrast studies are needed, and for confirmation urinary iodine measurement is helpful. Transient thyrotoxicosis states are treated with nonselective beta-blockers such as propranolol (Table 1.3).

Thyrotoxicosis with Low Thyroid RAIU and Low Serum Thyroglobulin

Iatrogenic and factitious thyrotoxicosis is associated with low RAIU [1]. In the presence of small thyroid size and thyrotoxicosis associated with very low thyroid RAI uptake and absence of iodine contamination, if factitious thyrotoxicosis is suspected, a very low serum thyroglobulin should suggest exogenous factitious or inadvertent thyroid hormone intake,

even if patient does not volunteer the history. If thyroglobulin antibodies are positive, they interfere with the assay, and low thyroglobulin is not reliable. It should be noted that serum thyroglobulin may be normal if patient has preexisting nodular goiter concurrent with excess thyroid hormone intake. Herbal supplements for weight loss presumably containing thyroid hormone have been reported with thyrotoxicosis [20]. Consumption of hamburger and sausages containing thyroid tissue has also been associated with exogenous thyrotoxicosis in some reported cases [21].

Thyrotoxicosis Presenting with Neck Pain

Three conditions may present with thyroid pain and thyrotoxicosis: the most common is granulomatous thyroiditis or de Quervain's thyroiditis [22], most likely a viral condition. It usually follows an upper respiratory infection, is associated with a febrile illness, and presents with exquisite thyroid pain and tenderness radiating to ears and very firm and irregular thyroid. One lobe can be involved first followed by the other. Thyroid hormone levels are elevated, TSH is suppressed, RAIU is close to zero, sedimentation rate is high, blood count is normal, and serum thyroglobulin level is elevated [22]. Hyperthyroid phase is followed by a transient hypothyroid phase and less commonly (in 5–15%) by permanent hypothyroidism. The process lasts few months. Management of thyrotoxicosis is by nonselective beta-blockers (Table 1.3) and nonsteroidal anti-inflammatory agents (NSAIDS) and in severe cases with a short course of glucocorticoids. Recurrence may occur in 2–5% after several years [22].

The second cause of painful transient thyrotoxicosis is bleeding into a functioning nodule resulting in release of stored hormones. This will be unilateral with distinct palpable nodule. ESR is normal, radioactive iodine uptake is low, and serum thyroglobulin levels are extremely high. Diagnosis is by thyroid ultrasound showing cystic development in a nodule as a result of bleeding. Symptoms are usually mild; pain has a short duration. Duration of hyperthyroidism is also shorter than subacute thyroiditis [23].

The third cause is rare association of thyrotoxicosis with suppurative thyroiditis. Bacterial infection of thyroid and abscess formation are rare. Infection may occur after procedures or spontaneously and also from infected piriform sinus fistula [24]. It is associated with fever and local inflammatory signs and symptoms and abnormal blood count. Diagnosis is with neck ultrasound showing abscess formation. Fine needle aspiration (FNA) and culture establish the infectious etiology. Thyrotoxicosis is usually short-lived and may be masked by inflammatory and systemic symptoms [24, 25]. Management is management of infection and beta-blocker for thyrotoxicosis symptoms.

Drug-Induced Thyrotoxicosis and Hyperthyroidism

Iodine-containing contrast media can cause iodine-induced hyperthyroidism particularly in iodine-deficient areas and in patients with nodular goiter. The duration depends on the half-life of clearance of exogenous iodine. In the case of radiologic contrast media, usually it will be a few weeks or months; in the case of amiodarone, it may be months to a year. Lithium [26, 27], denileukin diftitox [28], interferon gamma, pembrolizumab anti-PD-1 monoclonal antibodies (an immune checkpoint blocker) [29], pegylated interferon alfa-2b [30], and anti-cytokine therapies and biotherapies can cause transient painless thyroiditis that lasts weeks to few months and should be managed with beta-blockers and supportive care. Sometimes thyroid autoimmunity such as Graves' disease is induced by these medications. Tyrosine kinase inhibitors such as sunitinib and cabozantinib [31, 32] and thalidomide derivatives may cause thyroid dysfunction and sometimes thyroiditis with transient hyperthyroidism [31–33].

Amiodarone-Induced Thyrotoxicosis

This is one of the most difficult management problems in thyroid practice [34–36]. Patients usually have a critical and sometimes life-threatening cardiac arrhythmia. Amiodarone has high concentration of iodine and after discontinuation of therapy may stay in the body up to 6–12 months. Obtaining thyroid RAIU is not helpful for diagnosis because it is low due to a high iodine pool. Two types of thyrotoxicosis are recognized with amiodarone: Type I is iodine induced and is more common in iodine-deficient areas. Type II, a toxic destructive thyroiditis, is the more common type. Type I occurs usually in the background of nodular goiter [34, 35]. It is essential to differentiate these two types since therapies are quite different. Therapy of type I includes antithyroid drugs plus discontinuation of amiodarone if it is considered safe. Therapy of type II is with glucocorticoids. Ultrasound of thyroid is helpful in differentiation of these two: In type II, thyroid size is usually normal and gland is distinctly hypovascular [35]. The problem is that although most likely majority of the cases in the United States are type II, many cases are mixed and thyrotoxicosis develops as a result of both increased release and increased production of hormones. Although pure type II should respond to corticosteroids within 2–5 weeks, sometimes combination empiric therapy with methimazole along with corticosteroids is used. In this situation early response to corticosteroids and normalization of thyroid function within 2–5 weeks favor type II diagnosis. Amiodarone therapy should only be stopped if possible and safe, since iodine-induced type will continue

and type II thyroiditis may recur. Some cases may not respond to medical therapy, and in those surgery is a good option for rapid cure [36, 37].

Subclinical Hyperthyroidism

Subclinical hyperthyroidism is defined by lower than normal serum TSH, not explained by other causes such as pituitary disease, medications and acute illness, and normal levels of T3 and T4 [3]. This condition is more common than overt symptomatic hyperthyroidism. Etiologies are similar to clinical hyperthyroidism and thyrotoxicosis. It is present in mild Graves' disease or in early-stage toxic nodular goiter. Approximately 50% of subclinical hyperthyroidism cases have subtle symptoms such as increased pulse rate. Symptoms are usually absent if TSH is >0.1 mIU. Younger individuals may tolerate the condition without adverse effects, but in postmenopausal women increased bone loss is the consequence. Individuals older than 60 years have three times higher likelihood of atrial fibrillation [38]. There is some epidemiologic evidence suggesting increased mortality with persistent serum TSH levels <0.5 in this age group. Thus confirmed subclinical hyperthyroidism should be treated in this group [39, 40]. Therapy depends on etiology. In cases of toxic adenoma or multinodular goiter, resolution of subclinical hyperthyroidism is unlikely, and definitive therapy with radioactive iodine or surgery should be recommended. More than one abnormal test over time is needed before intervention.

Transient causes such as silent and subacute thyroiditis can be managed by beta-blockers while waiting for resolution. In subclinical Graves' disease, antithyroid and RAI therapy are equally effective. In younger age group, beta-blocker therapy alone or observation is acceptable [39].

Hyperthyroidism Associated with Pregnancy

Differentiation of physiologic gestational thyrotoxicosis from hyperthyroidism in the first 3 months of pregnancy is important and often difficult [41]. Thyroid is stimulated by human chorionic gonadotropin (HCG). TSH may be low or even suppressed, and symptoms may also be misleading. Very high levels of free T4, presence of goiter, and positive TRAB are helpful for diagnosis. Preexisting Graves' disease may improve during pregnancy and may relapse after childbirth. Treatment of hyperthyroidism is PTU in the first 3 months because of teratogenic effect of methimazole [2, 42], but after the first trimester, PTU can be switched to methimazole because of its lower side effect profile. Total T4 should be kept 1.5 times above the upper limit of normal and free T4 at the upper limit of normal to prevent fetal hypothy-

roidism. Surgery can be done in the second trimester if there are adverse reactions to antithyroid therapies, or large doses of antithyroids are required for control of hyperthyroidism [43]. In mild cases of Graves' disease under antithyroid therapy, discontinuation of antithyroid therapy and observation in the onset of pregnancy may be a consideration (2).

There is no evidence that subclinical hyperthyroidism has adverse effect in pregnancy for the fetus or the mother; thus therapy is not recommended [43].

Fetal and Neonatal Hyperthyroidism

Because TRAB crosses the placenta and can affect fetal thyroid, these antibodies should be checked at weeks 18–22 in pregnant patients with current or previous history of Graves' disease or a history of neonatal Graves' or previous elevated TRAB [2]. If TRAB is positive at 2–3 times above normal, fetal thyroid should be monitored by ultrasound at 18–22 weeks and repeated every 4–6 weeks. Evidence of fetal hyperthyroidism is goiter, hydrops, advanced fetal bone age, increased pulse, and cardiac failure. In this case even if the mother is euthyroid on thyroxine therapy, antithyroids should be given with close monitoring. Neonatal hyperthyroidism is fortunately temporary, but short-term antithyroid therapy for the newborn may be needed [2].

Hyperthyroidism in Pediatric Age Group

In this age group, the cause is usually Graves' disease, and The American Thyroid Association guidelines recommends avoidance of RAI therapy in children younger than age 5, and in this group methimazol therapy or surgery in the hands of high volume surgeons is recommended.

ATA guidelines allow RAI therapy as an acceptable therapy in some older children with certain conditions [2]. However, most clinicians prefer long-term antithyroid therapy and (avoiding PTU) in some persistent cases thyroidectomy.

Hyperthyroidism in Trophoblastic Disease

HCG and TSH have similarities in their structure and receptors. Thus in the first trimester of pregnancy, TSH levels are low and have inverse relationship with HCG levels. Mild physiologic thyrotoxicosis by HCG stimulation may be present that may be more pronounced in hyperemesis gravidarum [44]. Very high levels of HCG in hydatidiform mole and choriocarcinoma can present with significant hyperthyroidism and even thyroid storm [44, 45]. Treatment is management of the trophoblastic condition and antithyroid therapy.

Hyperthyroidism with Inappropriately Normal Serum TSH in TSH-Producing Pituitary Adenoma

In the presence of inappropriately normal serum TSH with elevated thyroid hormone levels and symptoms of hyperthyroidism, laboratory artifacts such as heterophile antibodies and abnormal binding to proteins should be excluded, as should thyroid hormone resistance. An MRI of pituitary should follow. Elevated beta-subunit will be in favor of TSH-secreting pituitary adenoma causing hyperthyroidism. These cases are very rare [2].

Hyperthyroidism in Thyroid Hormone Resistance

Most adult patients with generalized thyroid hormone resistance have elevated peripheral thyroid hormone levels and inappropriately normal serum TSH and have clinical thyroid [46]. If there is pituitary thyroid hormone resistance or if the degree of resistance is higher in the pituitary than in the peripheral tissues, hyperthyroidism may occur [47]. Diagnosis of this rare condition is difficult and should be guided by clinical evaluation surrogates of excess thyroxine effects such as sex hormone-binding globulin (SHBG) may be useful.

Thyrotoxicosis Associated with "Café au Lait" Pigmentation and Fibrous Dysplasia (McCune–Albright Syndrome)

In this syndrome associated with polyostotic fibrous dysplasia and "café au lait" pigmentation, because of constitutive activation of G(s) alpha by inhibition of its GTPase, non-autoimmune hyperthyroidism may develop and may be associated with nodular goiter. In this rare syndrome, treatment is surgery or RAI ablation. Remission with antithyroid medications does not occur [2].

Non-autoimmune Hyperthyroidism Caused by Genetic Mutation of TSH Receptor

Germline-activating mutation of TSH receptor is a rare cause of hyperthyroidism in infancy and childhood. Best treatment after preparation with antithyroid medications is surgery at appropriate age. In adult patients RAI therapy can also be considered [48]. Activating mutations can also result in toxic adenoma that may present in adulthood.

Metastatic Follicular Cancer and Hyperthyroidism

Thyrotoxicosis is rarely a presenting picture in widespread metastatic follicular cancer. Occasionally it may present after excision of the primary tumor and may resolve with radioactive iodine therapy or excision of bulky tumors or tyrosine kinase inhibitor therapy [49]. It also can present with T3 toxicosis because of high rate of conversion of exogenous T4 to T3 of the therapeutic administered T4 by tumor that expresses high di-iodinase [50].

Hyperthyroidism Associated with Normal T4 but Elevated T3 (T3 Toxicosis)

It is doubtful that T3 toxicosis is a distinct entity [2]. In the early phase of hyperthyroidism, only T3 elevation may be present, and T4 elevation occurs later. It is conceivable that in iodine-deficient areas and in certain conditions, more T3 than T4 may be produced. Patients with hyperthyroidism on antithyroid therapy and after failure of RAI therapy may have normal free T4 and elevated free T3.

Patients on excess thyroid extract therapy also have T3 toxicosis which can be associated with normal or low free T4, suppressed TSH, and elevated free T3 levels. This is due to excess T3-to-T4 ratio in the commercial thyroid extract products. Thus in patients with thyroid extract therapy, measurement of peripheral hormones does not correlate with thyroid function status, and TSH measurement is the definitive test for assessment of therapy.

Laboratory Investigation of Thyrotoxicosis and Hyperthyroidism

Although the first and most sensitive test in the presence of normal pituitary function is serum TSH, it is only an indirect measure of thyroid function, and when thyrotoxicosis is suspected, circulating hormone levels such as free T4 and free T3 should be measured [2]. First, free T4 should be measured, and, if normal, measurement of free T3 should follow. To differentiate between the two main categories of high and low RAIU thyrotoxicosis, thyroid RAIU should be measured next [2]. Thyroid scan usually is not needed except for cases of nodular disease with hyperthyroidism [2]. Ultrasound is sometimes helpful in the differential diagnosis. Ultrasound identifies nodule size, number of nodules, and vascularity. Increased vascularity in a diffuse goiter suggests Graves' disease, whereas low vascularity is seen in cases of destructive thyroiditis such as type 2 amiodarone-induced hyperthy-

roidism [34]. Also in cases of Graves' disease, associated significant conditions such as occult malignancy change the management. When there is doubt about the etiology and also for prognostic assessment and monitoring of antithyroid therapy effectiveness, measurement of TRAB is helpful [2, 8]. Thyroid-stimulating immunoglobulin assay (TSI), a bioassay, is more expensive and is being replaced by immunoassay of TRAB.

Management of Thyrotoxicosis and Hyperthyroidism

For transient conditions such as silent, subacute, and post-partum thyroiditis and all conditions associated with the release of stored thyroid hormones, symptomatic therapy with nonselective beta-blocker medications (Table 1.3) is adequate as noted previously [2]. Two major and common causes of hyperthyroidism, Graves' disease and multinodular toxic goiter, require more detailed discussion.

Management of Graves' Hyperthyroidism

Nonselective beta-blockers, if not contraindicated, will improve most symptoms and can be continued until hormone levels are normalized by specific therapy [2]. Hyperthyroid patients may require relatively high doses, and 120–240 mg/day of propranolol and equivalent other beta-blockers may be needed (Table 1.3). If beta-blockers are contraindicated, calcium channel blockers can be used [2].

Choice of modality of definitive therapy for Graves' hyperthyroidism should be based on severity of hyperthyroidism, patient preference, and age of the patient.

Pediatric patients deserve a 1.5–2-year course of antithyroid medication [2, 51]. Longer-term antithyroid therapies are also a possibility. Methimazole is the drug of choice for all patients especially for pediatric age due to recent reports of life-threatening liver toxicity with (propylthiouracil) PTU [2, 51]. In pediatric patients if antithyroid medications are not tolerated, thyroidectomy would be an option. However, despite hesitancy to use in children, it should be noted that RAI therapy in pediatric group has not been associated with long-term adverse effects [2, 52].

In adults, one of these three choices should be presented to the patient: antithyroid drugs, radioactive iodine, or surgery [2]. None of these modalities addresses the basic autoimmune process in Graves' disease, although a mild immunosuppressive action is suggested for antithyroid medications. Theoretically, and based on some studies, a near-total thyroidectomy eliminates the source of thyroid antigen the fastest. RAI therapy increases the release of antigen hence TRAB levels in the first few months, but if total thy-

roid ablation is done eventually, the antigen source will be decreased, hence resulting in decreased antibodies later on, and there may be long-term benefit.

Pros and Cons of Antithyroid Therapy

Antithyroid therapy for 18 months results in only a 50% remission rate. This is an argument in favor of thyroid-ablative modalities such as RAI, in particular in older individuals and in patients with comorbidities [2]. Patient should also be counseled about possible side effects of antithyroid therapy, such as skin allergy and a 1/1000 likelihood of agranulocytosis and pancytopenia [53], liver toxicity particularly with PTU [54], and rare cases of ANCA-positive vasculitis and lupus-like syndrome [55]. However some patients who want to avoid lifelong thyroxine therapy after ablative therapies prefer to use antithyroid drugs. The majority of endocrinologists in the United States traditionally have chosen RAI therapy as the preferred definitive therapy in adults [2]. However the trend is changing to some degree in favor of antithyroid therapy [2].

If antithyroid therapy is chosen, drug of choice is methimazole with a starting dose of 20–30 mg daily which can be given in once-a-day program [2, 55]. Prior to initiation of therapy, a blood count and white count with differential and liver function tests such as transaminase and bilirubin should be obtained [2]. When thyroid functions normalize with therapy, which is usually in 5–8 weeks, maintenance dose of 5–10 mg will be usually adequate. Therapy should be continued for 18 months, and, at that point if thyroid function is normal; it can be stopped [2]. Under certain conditions and for patients with reduced life expectancy, nursing home patients, in pediatric age group, and if patient does not accept ablative therapy, antithyroid therapy can be continued for a longer period of time [2]. TRAB measurement 6 months after antithyroid therapy may predict the rate of remission or relapse and is recommended by ATA [2].

Monitoring of antithyroid therapy is by measurement of free T4, and T3 and liver function tests initially, and TSH, free T4, and liver function tests thereafter periodically. Blood count does not seem to predict impending agranulocytosis since it can happen in between tests. Advising patient to stop medication in case of complications, fever, and sore throat and obtaining a complete blood count with differential at that point are more helpful [2]. It should be noted that hyperthyroidism can cause mild leukopenia and also abnormal liver function tests, hence the need for baseline studies. If initial transaminases are more than five times, normal antithyroid therapy should not be initiated [2]. Measurement of TRAb levels prior to stopping ATD therapy is suggested because it aids in predicting which patients can be weaned from the medication, with normal levels indicating greater chance for

remission [2]. Minor skin reactions can be transient, but significant skin allergies should result in discontinuing medications. At that point alternate therapies or switching to PTU should be considered. However because of cross-reactivity in the case of minor skin reactions, it may be best to choose RAI or surgery.

How to Manage Recurrence of Hyperthyroidism After 18 Months of Antithyroid Therapy?

In adults, ablative therapy, preferably RAI therapy, is usually recommended. For women with pregnancy planned in the next 6 months, surgery may be a better choice. Surgery, with the availability of a high-volume experienced surgeon, may be suitable for patients with large goiter who are at good surgical risk or have moderate-to-severe ophthalmopathy, because of concern about worsening of eye disease after RAI [2]. Long-term antithyroid therapy may be considered in very old patients or in children. Recent guidelines of ATA consider long-term antithyroid therapy as an acceptable option for patients [2]. This recommendation is based on recent studies providing evidence for safety and effectiveness of long-term antithyroid therapy. A recent meta-analysis of six studies with duration of therapy of 41–98 months showed remission rate of 57% [56]. Patient preference also should be a factor in decision [2].

Radioactive Iodine Therapy (RAI) for Graves' Hyperthyroidism

In some clinics this is the first choice for initial management of nonpregnant adults with Graves' disease who accept post-RAI hypothyroidism. RAI should be avoided in women who plan pregnancy in the next 6–9 months. But women who have no intention of pregnancy for 9 months but wish to have pregnancy after definitive management are also candidates for RAI therapy. Unavailability of a high-volume thyroid surgeon and failure of or intolerance to antithyroid therapy are also good indications for ablative radioactive iodine therapy. Obviously, pregnancy and lactation are absolute contraindications. If RAI is given, it should be with the intention of making the patient hypothyroid within 3–6 months and to be followed by lifelong thyroxine therapy. The dose of RAI must be proportional to the size of thyroid and degree of thyroid RAI uptake. The weight of thyroid estimated by palpation, or volume measured by ultrasound, can be used. In our clinic, we usually give 200 micro-Curie (uCi) per estimated gram of thyroid weight adjusted for 24-hr RAIU. Some authors suggest a fixed dose of 370 MBq for smaller thyroids and 555 MBq for larger goiters; however hypothyroidism

rate in a 12-month follow-up was 56% for the lower dose and 71% for the higher dose [57]. If same-day treatment is desired, a 4- or 3-hr [58] uptake can be obtained, and 24-hr uptake calculated. Prior PTU therapy reduces sensitivity to RAI, and for this group we give 250 uCi per estimated gram of thyroid weight. Methimazole may not reduce sensitivity to RAI. RAI dose should not be underestimated since the desirable hypothyroidism will be achieved sooner with higher doses. In our clinic with the above program, 90% of patients will be hypothyroid within 3 months. TSH and free thyroxine should be obtained in 2 months and 3 months.

Management Before and Immediately After RAI Therapy

Beta-blockers given before and for 4 weeks after RAI therapy are usually adequate [2]. Patients with severe thyrotoxicosis and patients with cardiac failure or with fragile health can be prepared with 3–4 weeks of methimazole therapy to reduce thyroxine levels to a safe range [59]. Antithyroid drug therapy should be stopped 3–5 days before RAI and can be restarted 3–5 days after RAI and continued for 4 weeks. Thyroid storm is rare after RAI, but worsening of symptoms if significant should be reported and approbate measures such as adjustment of beta-blockers, stable iodine, or short course corticosteroids be given.

Surgical Management of Graves' Hyperthyroidism

Surgery with near-total thyroidectomy, rendering patients hypothyroid and placing patients immediately on thyroxine therapy in the hands of experienced thyroid surgeon, is a safe and effective treatment for Graves' disease [60]. It is an option for patients with very large goiters or with associated nodular disease, for patients with suspicious nodules in the thyroid, and for patients not responding to antithyroid therapy that do not want or are not candidates for RAI therapy. Pediatric age group patients with failure or intolerance to antithyroid therapy [61, 62] are also candidates. Pregnant women with poor response to antithyroid therapy are also candidate for surgery in the second trimester of pregnancy. Patients with significant ophthalmopathy may also be candidates for surgery since it has been shown that after surgery TRAB decreases, whereas they increase with RAI therapy alone in the first year [2]. There is also 15% possibility of worsening of ophthalmopathy, 5% being permanent, if corticosteroid therapy is not given for 2–3 months concurrently [63]. Thyroidectomy for Graves' hyperthyroidism should be done only by a high-volume endocrine surgeon.

Preparing Patients with Graves' Hyperthyroidism for Surgery

Although mild cases can be prepared with beta-blockers and iodide (few drops of Lugol's solution or SSKI in water or juice three times a day for 10 days prior to surgery) [2, 64], usually it is best to normalize or significantly improve thyroid function with methimazole prior to surgery. With these precautions postoperative thyroid storm can be avoided. Iodine reduces vascularity as well as release of thyroid hormones from the gland.

To reduce the rate of post-surgical significant hypocalcemia, ATA suggests that calcium and 25-hydroxy vitamin D should be assessed preoperatively and repleted if necessary or given prophylactically. Calcitriol supplementation should be considered preoperatively in patients at increased risk for transient or permanent hypoparathyroidism [2].

Management of Severe Hyperthyroidism and Thyroid Storm

Severe life-threatening thyrotoxicosis can occur in patients with associated non-thyroid-related acute conditions such as infection, rarely after radioactive iodine therapy, abrupt cessation of antithyroid therapy in severe cases, thyroid or non-thyroid surgery, and in unrecognized and untreated patients [2, 64]. Thyroid storm manifests by arrhythmia, heart failure, hyperpyrexia, dehydration, hypotension, vomiting, diarrhea, confusion, agitation, stupor, and occasionally coma [65]. This is a true endocrine emergency and should be managed in intensive care setting [2] with hydration, cooling, respiratory support, and management of arrhythmia and cardiac complications. Thyroid hormone synthesis should be blocked by high-dose antithyroids (60 mg of methimazole or 600 mg of PTU) followed by inorganic iodide drops to stop release of thyroid hormones. Intravenous corticosteroid therapy is usually needed. Plasmapheresis has been used effectively in some cases [66]. Some cases of severe hyperthyroidism at risk of thyroid storm, but not yet in crisis, can be treated with combination of above modalities in outpatient setting with close observation.

Management of Toxic Adenoma and Toxic Multinodular Goiter

Comprehensive guidelines for management of toxic adenoma and toxic multinodular goiter are well outlined elsewhere [2].

In single toxic adenoma, surgery is more appropriate for larger toxic nodules, younger patients, patient desire for a rapid cure, desirability of less than 1% incidence of postsurgical hypothyroidism as opposed to 3–20% for radioactive iodine therapy, and 100% rate of cure of hyperthyroidism as opposed to 80% for radioactive iodine [2]. Availability of experienced thyroid surgeon, absence of comorbid conditions, and increased risk of surgery should be taken into account. RAI on the opposite is more appropriate for older patients, smaller nodules in younger individuals [2].

For toxic multinodular goiter (Plummer's disease), same factors should be considered. However, in multinodular disease the rate of hypothyroidism after thyroidectomy is 100% and is low after radioactive iodine therapy [2]. Compressive symptoms and presence of nodules with risk of malignancy will be an indication for surgery. Antithyroid medications are not appropriate for long-term therapy of nodular toxic disease except for individuals with decreased life expectancy or increased risk factors for other modalities. In general antithyroids are not recommended except for preparation for surgery or in some cases prior to radioactive iodine therapy. Beta-blockers are usually adequate pre-therapy and post-therapy for radioactive iodine and pre-therapy for surgery. For patients receiving RAI therapy, isotopic thyroid scan should be available since nonfunctioning nodule will need FNA for confirmation of benign nature prior decision for RAI therapy [2]. ATA suggests that alternative therapies such as ethanol or radiofrequency ablation of TA and TMNG can be considered in select patients in whom RAI, surgery, and long-term ATD are inappropriate, contraindicated, or refused and expertise in these procedures is available [2].

Management of Hyperthyroidism Associated with Ophthalmopathy and Thyroid Dermopathy

Management of hyperthyroidism in the presence of ophthalmopathy is a matter of debate [67]. Surgery, and to a lesser degree antithyroids, reduces the receptor antibody levels, whereas RAI if not given with concomitant corticosteroids may increase the TRAB in the first year. Tobacco cessation in smokers and rapid achievement of euthyroidism are essential [67, 68]. In the absence of ophthalmopathy and in non-smokers, ATA guidelines recommend RAI therapy without concurrent corticosteroids. For mild ophthalmopathy and no risk factors for thyroid eye disease, ATA accepts all three modalities of therapy, but if radioactive iodine is chosen, concurrent corticosteroid treatment is recommended. However, ATA recommends antithyroid therapy or surgery for moderate-to-severe and sight-threatening ophthalmopathy [2]. Ablative therapy by radioactive iodine or surgery eliminates source of thyroid antigen and may have theoretical long-term benefit on the course of extra-thyroidal manifestations, but evidence is lacking.

Conclusions

Thyrotoxicosis is the general term for excess thyroid hormone action. Hyperthyroidism is when thyroid is producing and releasing excess hormones. The most common cause is Graves' hyperthyroidism, the next being toxic nodular goiter (Plummer's disease). There are also several rare causes of overproduction of thyroid hormones. In conditions when destructive process in the thyroid results in release of stored hormones, the term thyrotoxicosis is a better term, since thyroid is not overproducing hormones. In these conditions only symptomatic therapy is needed. For hyperthyroid overproduction category, either antithyroid medication or ablative therapies such as surgery and radioactive iodine are needed. Recent ATA guidelines recommend long-term antithyroid therapy as an option for some patients with Graves' disease and emphasize the importance of periodic TRAB measurement during antithyroid therapy as a guide for prediction of remission. Management of thyrotoxicosis syndromes should be tailored to the cause associated with autoimmune manifestations, age of the patient, and other clinical considerations and patient preferences.

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