Diagnosis and Treatment of Hyperthyroidism

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Abstract

This chapter deals with the current management of patients presenting with an excess of circulating thyroid hormones. This condition is known under two different words: hyperthyroidism and thyrotoxicosis describing two distinct pathologic conditions that should be recognized at diagnosis because they have a different natural history and may have different therapeutic approaches. The hypertiroidism indicates a condition determined by an excessive synthesis of thyroid hormones by the thyroid tissue, any cause. In the United States hyperthyroidism has a prevalence of approximately 1.2% of the population. The most common cause is Graves' disease (GD), followed by toxic nodular goiter, whose prevalence increases with age, particularly in the regions of iodine deficiency, or single hyperfunctioning thyroid adenoma (Plummer's adenoma) and, more rarely a TSH-producing pituitary adenoma. The thyrotoxicosis reflects any medical condition associated with high levels of thyroid hormones in the blood, secondary to destructive process of the thyroid or caused by improper intake of drugs or supplements containing thyroid hormones. In this manuscript the Authors report the main important condition of of hyperthyroidism and thyreotoxicosis, the current approaches for their diagnosis, and the options for the treatment of patients (medical treatments, radioisotopic treatment). The most important drugs used in the clinical practice are examined, and some clinical recommendations before particular treatments are reported.

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1.1 Introduction

The diagnosis and treatment of patients presenting with an excess of circulating thyroid hormones will be treated in this chapter. The excess of serum thyroid hormones (defined as hyperthyroidism and thyrotoxicosis) may depend on two distinct pathologic conditions that must be immediately recognized at diagnosis because they have a different natural history and they may have a different therapeutic approach. The word hypertiroidism indicates a condition determined by an increased synthesis of thyroid hormones by the thyroid gland, any cause. In the United States hyperthyroidism has a prevalence of approximately 1.2% of the population (0.5% subclinical, 0.7% overt). The most common cause is Graves' disease (GD), followed by toxic Nodular goiter (TMNG) whose prevalence increases with age, particularly in the regions of iodine deficiency, or single hyperfunctioning thyroid adenoma (Plummer's adenoma) and, more rarely, a TSH-producing pituitary adenoma. The word thyrotoxicosis is used to indicate any medical condition associated with high levels of thyroid hormones in the blood, secondary to destructive process of the thyroid or caused by improper intake of drugs or supplements containing thyroid hormones. The common conditions of hyperthyroidism and thyreotoxicosis are described in Table 1.1.

Table 1.1 Causes of excess of thyroid hormones

Conditions of hyperthyroidism	Conditions of thyrotoxicosis
Graves' disease	Amiodarone-induced thyrotoxicosis
Toxic nodular goiter	De Quervain's thyroiditis
HCG-induced gestational hyperthyroidism	Silent or painless thyroiditis (postpartum thyroiditis, drug-induced thyroiditis, hashitoxicosis)
Thyroid-stimulating hormone (TSH)-secreting pituitary adenomas	Factitious thyrotoxicosis
	Struma ovarii
	Hydatiform moles and choriocarcinoma

1.2 Conditions of Hyperthyroidism

1.2.1 Graves' Disease

GD is the most common autoimmune disease, affecting 0.5% of the population in the US, and represents 50–80% of cases of hyperthyroidism. It occurs more commonly amongst women, smokers and patients with other autoimmune diseases or a family history of thyroid autoimmunity. Peak incidence occurs between 40 and 60 years of age but any age group may be affected [1].

It is caused by an immune defect in genetically susceptible individuals in whom the production of specific auto-antibodies against the TSH-receptor (TRAb) results in thyroid hormone excess and glandular hyperplasia. This IgG antibodies bind to and activate TSH receptor on the surface of thyroid follicular cells. This activation stimulates follicular cell growth, causing diffuse thyroid enlargement and increased production of thyroid hormones with an increase in the fraction of triiodothyronine (T3) and thyroxine (T4).

When unrecognized Graves' disease impacts negatively on quality of life and poses serious risks of tachyarrhythmia and cardiac failure. Beyond the thyroid, Graves' disease has diverse soft-tissue effects that reflect its systemic autoimmune nature. Thyroid eye disease (Graves orbitopathy) is the most common of these manifestations, affecting up to 50% of patients with Graves' disease. Characteristic features of thyroid eye disease are chemosis, eyelid oedema and retraction, swelling, exophthalmos, corneal lesions and diplopia [2].

The onset of Graves' disease is usually acute, reflecting the sudden production of stimulatory TSH-receptor antibodies, but may be indolent or subacute. Patients report the classical symptoms of hyperthyroidism that include weight loss despite increased appetite, heat intolerance, irritability, insomnia, sweatiness, diarrhoea, palpitations, muscular weakness and menstrual irregularity. Clinical signs include diffuse goitre, fine resting tremor, tachycardia, hyperreflexia, eyelid lag, warm, smooth skin and proximal myopathy.

Older patients are more likely to present with subtle symptoms such as depression and weight

loss rather than overt symptoms of sympathetic overactivity. They are also more likely to present with cardiovascular features such as atrial fibrillation or congestive cardiac failure [3]. The measurement of serum anti-thyroid antibodies (anti-TPO and TRAb) are mandatory to confirm the diagnosis of Graves' disease. These antibodies, positive in 90% of patients with presumed Graves' disease, are measured as TSH-receptor binding (TBII) and stimulating antibodies (TSI), the latter reflecting the effect on thyroid function. The measurement of TSH-receptor antibodies may also have a role in assessing the risk of relapse after a course of thionamides for Graves' disease or when assessing the risk of neonatal Graves' disease in pregnant women with Graves' disease.

Technetium-labelled (^{99m}Tc—labeled) thyroid scintigraphy may aid diagnosis when the cause of hyperthyroidism remains uncertain. It effectively distinguishes Graves' disease from thyroiditis or an autonomously hyperfunctioning nodule, demonstrating diffusely increased uptake in Graves' disease, a focal area of increased uptake due to an autonomously hyperfunctioning nodule and diffusely reduced uptake in thyroiditis.

Real-time thyroid ultrasonography displaies characteristic and often striking features of Graves' disease including diffuse enlargement of the thyroid gland, marked increase in glandular vascularity and the presence of small hypoechoic patches that reflect the inflammatory process. Although the prevalence of thyroid cancer is not increased in patients with Graves' disease, a nodule that has suspicious features, such as hypoechogenicity, irregular edges or microcalcification, should be biopsied.

The three treatment modalities for Graves' hyperthyroidism include the use of thionamides (antithyroid drugs), radioactive iodine (RAI) therapy or surgery. Patients in Australia, the UK and Europe are more likely than their North American counterparts to receive an initial course of thionamide therapy prior to the consideration of RAI [4]. Surgery has the highest long-term remission rate (95%) but is not without risks.

The two thionamides that have been in use since the 1940s are propylthiouracil (PTU) and methimazole (MMI). These drugs work by blocking the synthesis of thyroid hormone. PTU has the additional action of inhibiting peripheral conversion of T4 to the more active T3. These drugs may also possess immunosuppressive and anti-inflammatory properties, but this is controversial [5, 6].

Patients should be informed of potential side effects including rash, arthralgia, ANCA-positive vasculitis, hepatitis and agranulocytosis and should be advised to stop antithyroid drugs if any potential symptoms of agranulocytosis develop, such as fever, oral ulceration or painful throat. This rare idiosyncratic reaction affects 0.1–0.3% of patients on antithyroid drugs, occurs acutely without prior warning and is not dose related. MMI is the treatment of choice, particularly in children, because of less side effects compared to PTU. The last is the treatment of choice when dealing with pregnant women because it is associated with less frequent congenital anomalies in the offspring.

Whenever anti-thyroid drugs are not able to induce stable remission after a complete course or when a definitive cure is required, the other treatment options are RAI therapy or surgery, the so called "definitive treatments".

RAI may be given following an unsuccessful course of thionamides. Before RAI therapy, the patient must be rendered perfectly euthyroid with Thionamides, which are discontinued a few days before the administration of RAI. In patients with severe hyperthyroidism or those in whom persistent hyperthyroidism poses serious risks (such as the elderly or cardiac patients), beta blockers therapy is useful after RAI in order to control the transient (usually 2 weeks) thyrotoxicosis observed after RAI therapy. The dose of radioactive iodine to be administered should be sufficient to completely destroy the thyroid gland, rendering the patient permanently hypothyroid. The recommended dose is usually the maximum (15 mCi) that can be administered on an outpatient basis. Tretament should be associated with a 2–3 months therapy with low dose corticosteroids aimed to prevent the development of Graves orbitopathy induced by RAI therapy.

Surgery is indicated in the presence of big goiters, or when rapid ablation of the thyroid gland is required, such as in case of severe

Graves' ophthalmopathy or suspicious nodules. It is also considered when the patient refuse RAI administration. Surgery consists of total thyroidectomy and should be performed when the patient is perfectly euthyroid. There is some suggestion that thyroidectomy may prevent the later development of thyroid eye disease but this is anecdotal and should not be an indication for surgery in most patients.

Rituximab, a monoclonal CD20 antibody, has been advocated for the treratment of thyroid eye disease. However, its utility is limited by both cost and toxicity and, most of all, by the fact that its effect has not been reproduced in some prospective studies [7, 8].

1.2.2 Toxic Nodular Goiter

Thyroid nodules are frequent in clinical practice, occurring with a prevalence of 4% by palpation, 33 to 68% by ultrasound examination, and 50% on autopsy series.

As the initial step for evaluation of a thyroid nodule is measurement of serum thyroid stimulating hormone (TSH), it is not uncommon that the patient has low-suppressed TSh (subclinical hyperthyroidism) ort overt hyperthyroidism. In this setting, the thyroid nodule may represent a solitary hyperfunctioning thyroid nodule in an otherwise normal thyroid gland or within a multinodular goiter. Thyroid scintigraphy employs radioiodine (^{123}I, ^{131}I) or technetium-99m-(^{99m}Tc) pertechnetate in order to differentiate these diagnostic possibilities.

The distinction is important, because hyperfunctioning nodules—also referred to as "autonomous," "autonomously-functioning," or "hot" nodules—are thought to only rarely harbor malignancy, such that fine needle aspiration (FNA) is not ususally indicated in this circumstance but need a treatment.

Total thyroidectomy or radioiodine therapy represent the treatments of choice for autonomous functioning solitary nodules but also in case of multinodular goiter. RAI is indicated provided that there are no compressive symptoms. Long-term anti-thyroid drugs are not recommended. RAI may also be preferred in elderly patients with significant comorbidities, previous surgery to the neck or with a small goiter. In multinodular goiter, non-functioning nodules should be submitted to FNAC, before surgery or RAI, to rule out malignancy.

1.2.3 HCG-Induced Gestational Hyperthyroidism

Gestational transient thyrotoxicosis of non-autoimmune origin is a rare condition caused by stimulation of the TSH receptor by placental hCG. May occurs in about 1.4% of pregnant women, mostly when hCG levels are above 70–80,000 IU/l.

hCG and TSH share the common glycoprotein alpha subunit and the beta subunit is highly homologous. At high doses, hCG cross-reacts with the TSH receptor, and this stimulation can lead to an increase in secretion of T4 and T3, with subsequent suppression of TSH secretion [9]. The thyroid gland of normal pregnant women may be stimulated by hCG to secrete slightly excessive quantities of T4 and induce a slight suppression of TSH, but it only induces overt hyperthyroidism in a subset of pregnant women. The increased secretion of hCG result in the physiological decrease in TSH levels that are characteristic of the first trimester of pregnancy, or in overt hyperthyroidism [10].

When hyperthyroidism is mild, the signs and symptoms of hyperthyroidism are not specific and overlap with those of normal pregnancy. Because of the decrease in the levels and bioactivity of hCG later in pregnancy, hCG-induced gestational hyperthyroidism is usually transient and limited to the first 3–4 months of gestation. In a subset of women, the manifestations of hCG-induced hyperthyroidism are more severe and they are often associated with hyperemesis. Hyperemesis patients had significantly greater mean serum levels of hCG, free T4, total T3, and estradiol, and lesser serum TSH concentrations compared to controls. The degree of biochemical hyperthyroidism and hCG concentration correlated directly with the severity of vomiting. The

hyperemesis may be caused by a marked hCG-induced increase in estradiol levels. However, the relation between hyperemesis and gestational hyperthyroidism varies among patients, and unidentified mechanisms may be involved.

The diagnosis is established by measuring TSH, free or total T4, and T3. The physiological decrease in TSH levels and the increase in total thyroid hormone concentrations associated with the increase in thyroxine-binding globulin (TBG) have to be considered when interpreting the results. TBG levels increase in response to elevated estradiol levels and plateau by about 20 weeks of gestation [11]. Treatment with antithyroid medications is often not necessary. Women with hyperemesis need therapy with antiemetics. In patients in whom total T4 levels are higher than 1.5 times the upper reference range, therapy with antithyroid drugs may be indicated. Propylthiouracil (PTU) is the preferred medication during the first trimester of pregnancy. Overtreatment with antithyroid drugs can result in hypothyroidism in the fetus. Therefore, free T4 should be kept close or slightly above the normal range with the lowest possible dose of antithyroid drugs.

1.2.4 Thyroid-Stimulating Hormone (TSH)-Secreting Pituitary Adenomas

(TSH)-secreting pituitary adenomas are a rare cause of hyperthyroidism. They account for 0.5–3% of all functioning pituitary tumors and much less than 1% of all cases of hyperthyroidism [12].

The diagnosis should be considered in all hyperthyroid patients with detectable TSH, especially those with a diffuse goiter and no typical manifestations of Graves' disease.

TSH-secreting adenomas secrete biologically active TSH in a more or less autonomous fashion, and its biological activity varies considerably; as a result, serum immunoreactive TSH concentrations range from normal (albeit inappropriately high in the presence of hyperthyroidism) to markedly elevated.

TSH-secreting pituitary adenomas must be differentiated from the syndrome of resistence to thyroid hormone, a rare genetic condition, in which thyroid hormone levels are increased and TSH is inappropriately detectable due to mutation in the TSH receptor. Since the TSH-receptors are different in different tissue, the sign and symptoms may be very individual in different patients. Some patients may not be hyperthyroid, while others may have cardiac symptoms only.

The differential diagnosis is based on clinical presentation, a-subunit protein levels, imaging, and occasionally, the T3 suppression test and the TRH stimulation test.

Approximately 20–25% of the adenomas secrete one or more other pituitary hormones, predominantly growth hormone or prolactin co-secretion of TSH and prolactin is approximately five times more common in women than in men.

As well as typical symptoms and signs of hyperthyroidism patients with TSH pituitary adenoma may have symptoms related to the expanding tumor mass or to the other hormonal co-secretion: visual field defects, menstrual disturbances, headache, galactorrhea, symptoms of acromegaly.

When discovered, management of these tumors has traditionally been through transsphenoidal resection as first-line therapy. Treatment is often difficult because of its large size and common cavernous sinus involvement at presentation, the resection is often incomplete or the tumor recurs. Despite debulking, the remaining small component of the tumor continues to produce enough TSH to cause persistent hyperthyroidism.

Adjuvant therapy with somatostatin analogs and radiosurgery has been used to treat patients not in remission after surgery. Cosecretion of GH does not predict tumor response to somatostatin analogs. TSH-secreting adenoma treatment by somatostatin analogs can be reduced TSH and a-subunit levels with the restoration of a euthyroid state in the majority of patients with an intact thyroid. Three-quarters of patients also can improved visual field findings and nearly half had decreased tumor size [13].

Dopamine agonists have failed to control TSH-secreting adenomas, except those cosecreting PRL in which case a decreased tumor mass has been noted.

1.3 Conditions of Thyrotoxicosis

1.3.1 Amiodarone-Induced Thyrotoxicosis

Amiodarone is an anti-arrhythmic drug that commonly affects the thyroid, causing hypothyroidism or thyrotoxicosis. Amiodarone inhibits both thyroid hormone uptake into peripheral tissues such as the liver and the activity of the 50-monodeiodinase, which is responsible for the conversion of T4 to T3 in these tissues. The primary result is that serum levels of T4 rise and T3 fall. Changes in serum thyrotropin (TSH) are not uncommon and often occur within days of amiodarone administration, these alterations don't need treatment [14, 15].

Amiodarone-induced thyrotoxicosis (AIT) may develop early during amiodarone treatment, but it has been reported that AIT may develop even several month after amiodarone withdrawal, since amiodarone and its metabolites have a long half-life due to accumulation in several tissues, especially fat. This is the reason that in the case of amiodarone-induced adverse effects stopping the therapy usually has little short-term benefit.

AIT is more frequent in males than in females (M/F = 3/1) and occurs in 3% of patients treated with amiodarone in North America, but is much more frequent (up to 10%) in countries with a low iodine dietary intake. The signs and symptoms of AIT usually begin as a reappearance of the underlying cardiac disease state, such as arrhythmias or angina.

AIT is caused by excessive thyroid hormone biosynthesis in response to iodine load in autonomously functioning thyroid glands, in patients with a preexisting nodular goiter or Graves' disease (type 1 or AIT 1), or by a destructive thyroiditis typically occurring in normal glands (type 2 or AIT 2) [16].

Color flow Doppler ultrasonography is useful to differentiate between type 1 and type 2 AIT. Intra-thyroidal vascular flow is increased in type 1 AIT and reduced or absent in type 2, determination of anti-thyroid antibodies (TgAb, TPOAb, TRAb) are often useful to distinguish AIT type 1, but high levels of Tg and TPOAb have also been reported in 8% of type 2 AIT.

Differential diagnosis AIT, between the two forms is critical, since treatments are different.

Type 1 AIT should be treated with high doses of thioamides (20–40 mg/day of methimazole; or 400–600 mg/day of propylthiouracil) to block the synthesis of thyroid hormones. Potassium perchlorate can also be used to increase sensitivity of the gland to thyonamides by blocking iodine uptake in the thyroid. KClO4 should be used for no more than 30 days at a daily dose <1 g/day, since this drug, especially in higher doses, is associated with aplastic anemia. Once thyroid hormones are back to normal, definitive treatment of the hyperthyroidism should be considered. If thyroid uptake is sufficient (>10%) radioactive iodine can be used. Thyroid surgery is a good alternative. If thyrotoxicosis worsens after initial control, a mixed form type1-type 2 should be considered, and treatment for type 2 AIT should be started.

Type 2 AIT can be treated with prednisone, starting with an initial dose of 0.5–0.7 mg/kg body weight per day, and the treatment is generally continued for 3 months. If a worsening of the thyrotoxicosis occurs during the taper, doses should be increased again. Thioamides are generally not useful in type 2 AIT, but to consider in mixed form or in non responder. For patients with persisting hyperthyroidism surgery is the optimal choice. Beta blockers will be helpful in preparation for surgery.

1.3.2 De Quervain's Thyroiditis

Inflammatory disorders of the thyroid gland are divided into three groups according to their duration: acute, subacute and chronic. De Quervain's thyroiditis (also termed giant cell or granulomatous thyroiditis) is a subacute inflammation of the thyroid, which accounts for 5% of thyroid disorders. The etiology is unknown, but it is presumed to be due to viral infection and it usually appears 2 weeks after an upper viral respiratory infection.

Clinically, the condition is associated with severe pain that is aggravated during swallowing, usually localized to the anterior aspect of the neck and may radiate up to the jawor ear. In addition, tenderness of the thyroid gland upon palpation and small diffuse goiter are frequently present. Common initial clinical features and laboratory investigation results include fever, fatigue, mild thyrotoxic manifestations, suppressed thyroid stimulating hormone (TSH), and elevated erythrocyte sedimentation rate, the leukocyte count, C-reactive protein are normal or slightly elevated.

The natural history of granulomatous thyroiditis involves four phases: the destructive inflammation results temporarily in thyrotoxicosis followed by euthyroidism. After a transient hypothyroidism the disease becomes inactive and the thyroid function is normalized, rarely patients developed permanent hypothyroidism and need thyroxine replacement therapy (less than 1%). Ultrasonographic findings are diffuse or pseudonodular hypoechogenic structures with typical reduction of vascular flow [17, 18]. Clinical picture and laboratory results are the bases for the diagnosis, while radioiodine uptake and cytological diagnosis are often not required.

There is no special treatment, but high dose steroid should be given immediately to relieve the pain. Salicylates and nonsteroidal antiinflammatory drugs can be used in patients with mild or moderate forms of the disorder. In more severe forms of the condition, corticosteroids in suitable pharmacological dosage will generally cause a rapid relief of symptoms within 24–48 h. Prednisone may be initiated in dosages of 50 mg daily, with a gradual reduction in dosage thereafter over several weeks. Recurrences do appear in a small percentage of patients, necessitating restoration of a higher dose once again [19].

1.3.3 Silent or Painless Thyroiditis

Silent thyroiditis is characterized by lymphocytic infiltration and can lead to transient thyrotoxicosis and hypothyroidism. Although the disease was earlier considered to be a mild form of subacute (De Quervain's) thyroiditis, there is now convincing evidence that it is a lymphocytic thyroiditis. Many patients with silent thyroiditis have a personal or a family history of other autoimmune diseases, thereby indirectly supporting the concept that it is an autoimmune thyroiditis. There is no significant association with viral infections. There is a significant association with HLA genotype DR3. Postpartum thyroiditis is considered to be a form of silent thyroiditis occurring after delivery [20].

The duration of the thyrotoxic phase is variable, but for the most part, it lasted less than 1 year. The mean duration was 3.6 months (range 1–12.5). Symptoms began about 2 months preceding the initial evaluation. Exophthalmos and pretibial myxedema were absent. The thyroid gland is typically firm in consistency. Forty three percent of patients had a mild enlarged thyroid. The clinical course of the disease consists usually of an initial hyperthyroid phase, followed by a hypothyroid phase, and sometimes subsequent restoration of a euthyroid metabolic state.

Development of Graves' disease, after painless thyroiditis has been documented and TSH receptor antibodies have been found in these patients.

During the first phase of the disease, discharge of hormone from the inflamed thyroid results in increases in serum T4, T3 and a decrease in serum TSH. During this phase, there is no uptake of radioactive iodine in the thyroid. In patients with silent thyroiditis, antithyroglobulin antibodies and antimicrosomal antibodies are positive [21]. The echogenicity is decreased and a correlation between the decrease in the echo signal at the onset and nadir of the T3 level has been suggested [22].

As thyrotoxicosis is usually mild in silent thyroiditis, there is often no need for any treatment. In some patients, therapy with a beta-blocker can be considered during the thyrotoxic phase. In patients with more severe thyrotoxicosis, administration of NSAIDs and prednisone may be of benefit [23]. After the thyrotoxic phase, many patients become temporarily hypothyroid and

therapy with levothyroxine should be initiated in symptomatic patients. After a few months, levothyroxine therapy should be gradually withdrawn in order to assess whether the hypothyroidism is transient or permanent. Only a small proportion of patients remain permanently hypothyroid. Some patients, who initially recovered, may ultimately develop permanent thyroid failure. In a series of 54 patients, Nikolai et al. reported that about half of the patients developed permanent hypothyroidism [24]. This is in contrast with subacute thyroiditis where permanent hypothyroidism is less common.

In this group of thyroiditis, we can consider some forms of drug-induced thyroiditis (cytokines, lithium, tyrosine kinase inhibitors) which may give destructive thyrotoxicosis, followed by hypothyroidism.

1.3.4 Factitious Thyrotoxicosis

Is due to the voluntary or involuntary intake of supraphysiological amounts of exogenous thyroid hormone. Most commonly, it is iatrogenic, either intentionally in order to suppress TSH in thyroid cancer patients or unintentionally in patients treated for primary hypothyroidism. In both instances, subclinical thyrotoxicosis is more common. The risk of atrial fibrilliation is increased in patients with long-standing suppression of TSH. Several cardiac parameters can be affected, but the severity of these effects is somewhat controversial. Suppressive doses of thyroid hormones can also affect bone mineral density, but this has not been confirmed in all studies. Non-iatrogenic thyrotoxicosis factitia can occur in patients of all ages with psychiatric illnesses. In addition, some patients may take excessive amounts of thyroid hormones, sometimes prescribed by physicians, for weight loss, treatment of depression, or infertility. These patients often deny the intake of thyroid hormones or an excessive intake. In these instances, a heightened suspicion is needed in order to readily diagnose the disorder. Thyrotoxicosis induced by excessive thyroid hormone intake due to consumption of meat containing bovine thyroid tissue has been reported repeatedly. Patients are clinically thyrotoxic, without signs of endocrine ophthalmopathy. The thyroid may be small because of long-standing suppression of TSH.

Serum TSH is suppressed, (free) T4 and T3 levels are variably elevated. The T4 and T3 levels depend on the type of ingested thyroid hormone preparation. Poisoning with T3 may be particularly severe, but even very high doses are often well tolerated, especially by children. When the diagnosis of thyrotoxicosis factitia is suspected, measurement of serum thyroglobulin levels is useful. During ingestion of levothyroxine, little or no thyroglobulin is present is necessary to exclude the presence of thyroglobulin antibodies that can potentially interfere with the assay. The thyroidal uptake of radioiodine or technetium are decreased like in silent thyroiditis but, in this, the serum thyroglobulin is elevated.

In most patients, adjustment or discontinuation of the thyroid hormone preparation is sufficient to normalize thyroid function tests. Patients with surreptitious intake of thyroid hormones for eating disorders or psychiatric illnesses can be difficult to treat and may need psychiatric consultation and assistance. In patients with severe intoxication, beta-blockers can be useful.

1.3.5 Struma Ovarii

Is a rare tumor consisting primarily of thyroid components occurring in a teratoma or dermoid in the ovary (1% of all ovarian tumors and 2–4% of all ovarian teratomas) 5–10% are malignant [25]. Thyrotoxicosis occurs in about 8% of affected patients. Thyroglobulin is secreted by benign and malignant ovarian strumae. Radioiodine uptake will reveal uptake in the pelvis, while the uptake in the thyroid is diminished or absen. Imaging with computed tomography or magnetic resonance imaging will demonstrate of unilateral or bilateral ovarian masses [26]. CA125 may be elevated. Malignant thyroid tissue shows the characteristic patterns of papillary or follicular thyroid cancer and can be positive for mutations in BRAF [27]. Metastasis is

uncommon but has been reported. Unilateral or bilateral open or laparoscopic oophorectomy is the primary therapy. Thyrotoxic women should be treated with antithyroid drugs and, if needed, with beta-blockers prior to surgery. In the case of malignant lesions, the patient should undergo thyroidectomy followed by treatment with 131 iodine. The subsequent surveillance for residual or recurrent cancer does not differ from primary thyroid carcinomas.

1.3.6 Hydatiform Moles and Choriocarcinoma

Hydatiform moles and choriocarcinomas are gestational trophoblastic diseases that secrete high amounts of hCG and can cause hyperthyroidism. In men, choriocarcinomas can arise in the testis and cause hyperthyroidism by secreting hCG.

A correlation between serum hCG levels and thyroid stimulating activity in both serum and urine was found in women and men who had widely metastatic choriocarcinoma and marked hyperthyroidism.

Most women with hydatiform moles present with uterine bleeding in the first half of pregnancy. The size of the uterus is large for the duration of gestation, molar pregnancies can cause nausea and vomiting, pregnancy-induced hypertension or pre-eclampsia. The signs and symptoms of thyrotoxicosis are present in some women, but they may be obscured by toxemic signs. Women with choriocarcinomas present within 1 year after conception. The tumor may be confined to the uterus, more frequently it is metastatic to multiple organs such as the liver and lungs, among others. In men, choriocarcinomas of the testes is often widely metastatic at initial presentation. Gynecomastia is a common finding. Measurement of serum hCG concentrations is needed for the diagnosis of moles and choriocarcinomas, and hCG serves as a sensitive and specific tumor marker during therapy and surveillance. In women, hCG concentrations are significantly higher than those found during normal pregnancies. Ultrasonography of the uterus shows a characteristic “snowstorm” pattern.

Hydatiform moles are treated by suction rather than curettage. Serum T4, T3, TSH, and hCG levels normalize rapidly after removal of the mole [28].

Choriocarcinomas can be divided into two groups: a low risk group treated by monotherapy, most often with methotrexate or actinomycine D and a success rate close to 100% and an high risk group treated with polychemotherapy (etoposide, methotrexate, actinomycine D, cyclophosphamide, vincristine) with a response of about 86%. In patients that are not responding to chemotherapy, the 5-year survival rate is about 43%. Longitudinal measurement of hCG as specific and sensitive tumor marker is key for long-term surveillance.

1.4 The Differential Diagnosis of Hyperthyroidism and Thyrotoxicosis

Blood sampling for TSH has the highest sensitivity and specificity to reveal thyroid disease and it can be used as a screening test, but is not sufficient to define the entity of hyperthyroidism, for this is also required the determination of both FT4 and FT3, taking into account that there are forms of hyperthyroidism with prevailing T3 secretion.

The patient’s clinical examination is main to identify patients with increased cardio-vascular risks, complications, or more debilitated and symptomatic, which requiring a faster resolution of hormonal imbalance [29, 30].

1.4.1 Search the Etiology of Thyrotoxicosis

The determination of both TSH and thyroid hormones allows to detect rare forms of TSH-mediated hyperthyroidism, once has been excluded interference to the assay (Table 1.1). The relationship between T3 and T4 can be useful in understanding the causes of thyrotoxicosis:

(a) A gland overactive tends to produce more T3 than T4.

(b) T4 is usually higher than T3 in thyrotoxicosis factitia (by exogenous L-thyroxine), iatrogenic, or attributable to autoimmune thyroiditis.

The distinction of subacute thyroiditis is usually not difficult, thanks to painful swelling of the neck, intensely accentuated by palpation, and low-grade fever with elevated inflammatory indices.

When the etiologic diagnosis is not sufficiently clear with the aid of clinical presentation and biochemical tests, further examinations are recommended:

TSH receptor antibody (TRAb) sampling: If they exceeding normal limits, are diagnostic of GD, with lower costs and faster results than the determination of the radioiodine uptake. Indeed TBII (TSH-binding inhibition immunoglobulin) third generation dosages have very high sensitivity and specificity and are positive in 96% of patients with GD.

Thyroid ultrasound examination with vascular signal (*ecodoppler*): the presence of increased blood flow could distinguish GD from the destructive thyroiditis and, if we exclude thyroiditis, ultrasound examination will highlight the presence of thyroid nodules and their characteristics.

Thyroid scintigraphy (with 123I or 99Tc pertechnetate) is useful if the clinical presentation and ultrasound examination suggests a toxic adenoma (TA) or TMNG.

Determination of radioiodine uptake (RAIU) provides further information: absent in the case of subacute, silent or postpartum thyroiditis, improper ingestion of thyroid hormones, excess iodine, increased in all cases of glandular hyperfunction.

Thyroglobulin (Tg) sampling is useful only for detecting unaware or psychotic intake of exogenous thyroid hormones, in which case it is suppressed (consider that positivity of anti-thyroglobulin antibodies interfere with serum Tg) [31].

Determination of urine iodine when we suspect an excess of iodine.

1.5 Antithyroid Drugs

The antithyroid drugs are the first choice in GD. They are thioamides (propylthiouracil, thiamazole, and carbimazole) and the mechanism of action is the inhibition of thyroid peroxidase [32].

Thiamazole is the preferred drug in Graves' disease, especially with a good chance of complete disease remission. In some conditions, such as hyperthyroidism during pregnancy (except for the first trimester), elderly patients with multiple comorbidities, cardiological patients requiring prompt correction of hyperthyroidism, this is the only therapeutical option.

In hyperthyroidism related to multi nodular goiter or Plummer toxic adenoma, drug therapy may be considered before surgery or RAI therapy for the improvement of clinical signs of hyperthyroidism (Table 1.2).

Thiamazole is considered the first line therapy; it has several advantages over propylthiouracil, such as better efficacy; longer half-life and duration of action, and less severe side-effects.

The use of propylthioracil is preferred during the first trimester of pregnancy and in patients with minor adverse reactions to thiamazole, who refuse surgery or RAI therapy [6].

The goal of the therapy is to reach the normal thyroid function as quickly and safely as possible. These medications in adequate doses are very effective in controlling the hyperthyroidism and they might also have anti-inflammatory and immunosuppressive effects [33, 34].

Patients should be informed about possible side effects of these drugs and the necessity of

Table 1.2 Indications of RAI vs thyroidectomy in hyperthyroidism

RAI	Total thyrodectomy
High surgical risk	Goiter with compressive symptoms
Previous surgery or RT neck	Moderate to severe Graves' ophthalmopathy
Planned pregnancy beyond 6 months	Planned pregnancy before 6 months
Diffused struma or little nodules (low ATA risk)	Multiple nodules or suspected malignancy

informing the referring physician promptly. Minor side-effects such as pruritic rash, arthralgia, and gastrointestinal distress occur in about 5% of patients. In minor skin reactions, an antihistamine can be added to the therapy or in some cases the antithyroid drug could be replaced with another one. Major side-effects of ATDs are rare and they usually develops within the first 3 months of therapy.

Agranulocytosis is the most frequent major side-effect (annual incidence 0.1–0.3%); it requires the immediate withdrawal of the medication if the granulocyte count is less than 1000 cells/mm^3. When patients receiving ATDs present with fever or sore throat, chills, diarrhea, or myalgia, a white blood cell count should be obtained. Trial of another ATD is contraindicated in this circumstance because of the documented cross-reactivity. Other very rare haematological side-effects of ATDs include aplastic anaemia, thrombocytopenia, and hypoprothrombinaemia.

Another major side-effect is hepatotoxicity (0.1–0.2%); it can rarely present as acute liver failure, which is associated with propylthiouracil more frequently than with thiamazole (0.25 vs 0.08%), and might require liver transplant.

It is recommended to obtain a baseline complete blood count and a serum liver profile before the initiation of therapy [35].

The starting dose of thiamazole depends on the severity of the hyperthyroidism and the size of the thyroid gland and could vary from 10–15 to 20–40 mg daily. The equivalent dose of carbimazole is approximately 140% of that of thiamazole. Thyroid function should be checked 4–6 weeks after initiation of therapy and then every 2–3 months once the patient is euthyroid.

TSH might remain suppressed for several months, which is why serum T4 and T3 should be monitored to assess efficacy of therapy.

Once euthyroidism is achieved, a maintenance dose (thiamazole 5–10 mg daily, or propylthiouracil 50–100 mg daily) should be continued for at least 12–18 months.

In presence of fever or symptoms suggestive for side effects, blood count and a serum liver profile should be checked, especially in the first 3 months of therapy.

Therapy can be gradually reduced and then suspended when a stable euthyroidism is reached and maintained.

1.5.1 Therapy During Pregnancy

Hyperthyroidism during pregnancy should be adequately treated to prevent maternal and fetal complications.

The treatment of choice for overt hyperthyroidism in pregnant women is ATD; radioiodine treatment is not recommended. If ATDs are not tolerated, the alternative treatment is thyroidectomy, preferably in the second trimester of pregnancy. Hyperthyroidism should be treated with the lowest possible dose to keep mother's level of T4 and T3 at or slightly above the normal range and the TSH below the normal range for pregnancy. Current guidelines recommend the use of PTU in the first trimester of pregnancy, and to switch to MMI in the second trimester considering the possible higher risk of hepatotoxicity associated with the use of PTU [36].

The drugs are equally effective in the treatment of hyperthyroidism, and they all pass the placenta, which may lead to fetal hypothyroidism in late pregnancy. The major concern to the use of these drugs in early pregnancy is, however, the potential risk of birth defects, including aplasia cutis, choanal atresia, oesophageal atresia, and omphalocele, described with thiamazole administration; although less common, propylthiouracil has also been shown to be associated with birth defects in the face and neck, and urinary systems [37].

1.5.2 The Use of Beta-Blockers

Beta-adrenergic blockade is recommended in patients with symptomatic hyperthyroidism to control the peripheral effects of excess thyroid hormones, especially in elderly patients with heart disease or tachycardia. The β blocker therapy in addiction can slightly decrease T4 to T3 conversion. These drugs are contraindicated in patients with asthma or history of bronchospasm;

in these patients could be used calcium channel blockers as verapamil or diltiazem to reduce the heart rate [38].

1.6 Radioactive Iodine (^{131}I)

As reported above radioactive iodine (^{131}I) can be used as treatment of patients with of hyperthyroidism. The indcations of radioactive iodine therapy (RAI) are discussed in details in a dedicated session of this textbook (see Chap. 3). However in the following paragraphs are summarized some recommendations and patient's preparation for patients with hyperthyroidism candidate to radioisotopic therapy.

1.7 Clinical Recommendation and Preparation Before Radioactive Iodine Therapy in Hyperthyroidism

Radioactive iodine therapy is safe and cost-effective and can be the first-line treatment for hyperthyroidism due to Graves' disease, toxic adenoma, and toxic multinodular goiter [39–41].

RAI should be preferred in women planning a pregnancy in the future (more than 6 months following the therapy), patients with high surgical risk, previously neck surgery or neck external irradiation or failure to obtain a normal thyroid function with pharmacological therapy. The indications and contraincications of RAI therapy versus surgery are summarized in Tables 1.2 and 1.3.

Absolute contraindications to RAI therapy are: pregnancy, breastfeeding, planning pregnancy (within 6 months), inability to comply with radiation safety recommendations, thyroid cancer or suspicion of thyroid cancer.

Table 1.3 Contraindication of RAI vs thyroidectomy in hyperthyroidism

RAI	Total thyrodesctomy
Pregnancy or lactation	Pregnancy (in the second quarter)
Thyroid cancer	High surgical risk
Severe Graves' ophthalmopathy	No experienced surgeons
Inability to follow the safety recommendations	Thyroid storm

In GD RAI therapy is contraindicated in patients with active moderate-to-severe Graves' orbitopathy, while in mild active Graves' orbitopathy, radioactive iodine treatment should be followed by prophylactic steroid treatment [34]. Patients with inactive Graves' orbitopathy, but no risk factors, can be given radioactive iodine therapy without corticosteroids.

In patients with thyroid nonfunctioning nodules or with suspicious ultrasound characteristics, fine needle aspiration with cytological examination should be performed before RAI treatment and, if they are suspicious or diagnostic of thyroid cancer, radioactive iodine is contraindicated and surgery is recommended.

Medical therapy for hyperthyroidism should be optimized prior RAI therapy and b-adrenergic blockade should be considered even in asymptomatic patients who are at increased risk for complications due to possible transient worsening of hyperthyroidism. Pharmacological therapy should be discontinued 3–5 days before radioactive iodine therapy, then restarted 3–7 days later, especially in high risk patients, and withdrawn as soon as thyroid function normalizes.

Before treatment patient should be informed about avoid nutritional supplements or radiologic contrasts containing iodine and seaweeds for at least 1 week.

In women should be obtained a pregnancy test within 48 h prior the treatment and patients must be informed about the need to delay the conception for at least 6 months and until normalization of the thyroid hormones is established. No adverse effects were reported on the health of offspring of patients given radioactive iodine for hyperthyroidism before pregnancy.

During breastfeeding RAI should not be administered for at least 6 weeks after lactation stop to avoid active concentration of radioactivity in breast tissues; breastfeeding should not be resumed after treatment.

Thyroid function should be monitored at least every 6–8 weeks after treatment and levothyroxine replacement should be started as soon as

hypothyroidism occurs. The timing for the thyroid hormone replacement therapy should be determined by results of thyroid function tests, clinical symptoms, and physical examination.

In the 40% of patients with GD hypothyroidism occur within 8 weeks and more than the 80% within 16 weeks. In multinodular goiter and toxic adenoma the resolution of hyperthyroidism occurs in approximately 55 and 75% of cases respectively within 3 months and the average size reduction is about 45% in 2 years. In patients with a persistent hyperthyroidism after 6 months following RAI therapy, a retreatment sholud be considered.

With the development of hypothyroidism, TSH levels may remain suppressed for some months after the resolution of hypothyroidism and consequently they should not be used initially to determine the need for levothyroxine.

Until TSH level is suppressed the levothyroxine dose should be adjusted based on an assessment of free T4. The required dose may be less than the typical full replacement, expecially in the first period of therapy, due to the possibility of an underlying persistent thyroid function.

Overt hypothyroidism should be avoided, especially in patients with active Graves' orbitopathy and in patients with cardiac disease.

Once euthyroidism is achieved, lifelong annual thyroid function testing is recommended.

1.8 Clinical Recommendation and Preparation for Surgery in Hyperthyroidism

Surgery should be taken into account in GD not responding to drug therapy, with large nodules or large goiter, when radioiodine (RAI) therapy it is not useable (Table 1.3). In these cases the chosen procedure is total thyroidectomy. When thyroid nodules are present, cytological examination must be performed before surgery if they have suspicious ultrasonographic characteristics or if they are cold or not avid at scintigraphic examination.

In toxic multinodular goiter or toxic adenoma the most appropriate therapies are RAI or surgery, while the long-term drug therapy is chosen only in selected situations.

RAI may be preferred in elderly patients with significant comorbidities, previous neck surgery, a small goiter or the unavailability of an experienced surgeon. If there are cold nodules these have to be subjected to cytological examination before treatment. In the presence of large goiters with compressive symptoms, in the suspicion of thyroid tumor coexistence or when hyperthyroidism rapid correction is necessary, surgical therapy should be preferred. The chosen procedure should be total thyroidectomy in multinodular goiter, while in uninodular toxic adenoma, can be performed hemithyroidectomy.

Appropriate medical preparation before surgery is necessary to reach the euthyroidism condition; this therapy must be stopped immediately before the intervention.

In patients with GD is recommended preoperative treatment with a potassium iodide solution (Lugol's solution) for about 7–10 days before the operation at a dose of 5–7 drops three times a day. Preoperative Lugol solution treatment decreases the rate of blood flow, and intraoperative blood loss during thyroidectomy [42].

It is recommended to control calcium and vitamin D before surgery; several studies demonstrated that the pre-existing vitamin D deficiency is an additional risk factor for postoperative hypocalcemia; moreover the GD itself is a risk factor for post surgical hypocalcemia. In these patients a vitamin D supplementation before surgery can be considered for a demonstrated role in the reduction of the risk of postoperative transient hypocalcemia.

Levothyroxine therapy for hypothyroidism should be undertaken immediately after total thyroidectomy at replacement dose (approximately 1.5 mcg/kg). After 6–8 weeks TSH and FT4 must be checked to verify the adequacy of the LT4 dose.

After lobectomy replacement therapy should not be necessary but periodical checks of thyroid function are needed and therapy should be considered only in case of evolution in hypothyroidism (about 20% of cases).

After total thyroidectomy it is recommended to check the levels of serum calcium and PTH after 6 and 12 h after surgery, administering calcium and calcitriol if necessary. If the PTH is normal when the patient reaches the normocalcaemia, calcium and calcitriol may be gradually reduced up to the suspension.

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