

Thyroid Disease: Diagnosis and Management of Hyperthyroidism

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This short review article aims to provide updated information on the diagnosis and management of hyperthyroidism. A second article will focus on the management of hypothyroidism.

The most appropriate management of hyperthyroidism depends to a large extent on the proper diagnosis based on recognition of symptoms and signs of the disease followed by determination of the underlying pathology. Graves disease is the most common underlying pathology followed by thyroiditis, multinodular goitre, toxic adenomas and iatrogenic causes. Graves disease, toxic adenoma and toxic multinodular goitre may be treated by surgery, antithyroid drugs or radioactive iodine. Treatment for hyperthyroidism caused by thyroiditis is usually symptomatic as the condition is usually transient. Treatment is not always straightforward however, as in such cases of associated ophthalmopathy in Graves disease and in patients who are pregnant or breastfeeding. It is very important to plan appropriate treatment with the patient.

Thyrotoxicosis or clinical hyperthyroidism is due to the effects of surplus thyroid hormone and can be caused by different

disorders. Prevalence of hyperthyroid disease based on community studies has been estimated at 2% in females and 0.2% in males. Thus a family practice of 2500 patients is expected to have a prevalence of ten thyroid cases with one new case annually. The clinical diagnosis of an over active thyroid can be difficult as the initial clinical deviations from normal can be minimal.

Symptoms are caused by the thyroid hormone's stimulation of the enzymatic catabolic activity and increased sensitivity to catecholamines. Symptoms are usually more florid in younger patients, elderly patients may present with only cardiovascular signs such as atrial fibrillation and tachycardia, or with unexplained weight loss. Common symptoms and signs are listed in Table 1 with an emphasis on the differences in presentation between old and young patients.

Tests for thyroid disorders

Thyroid function tests

With the highly sensitive TSH assays it is now possible to distinguish suppressed TSH levels in hyperthyroid states from low but normal-low TSH levels in the euthyroid state. It should however be noted that tests on their own are not foolproof and should be interpreted with the clinical situation in mind. Serum tri-iodothyronine (T3) and free thyroxine (T4) measurements can be useful in suspected T4 toxicosis where serum T4 levels may be normal. T3 and T4 levels are also useful for monitoring patients on treatment for thyroid dysfunction.

Thyroid autoantibodies

Raised **antimicrosomal** and **antithyroid peroxidase** antibodies are indicative of **Hashimoto's** autoimmune thyroiditis. **Antithyroglobulin** and **antimicrosomal** antibodies are characteristically elevated in **Graves' disease**. Thyroid stimulating antibody (Thyroid-stimulating hormone receptor antibodies) levels are also used to monitor the effects of treatment of Graves' disease with antithyroid drugs.

Signs and Symptoms	Older Patients >70 years %	Younger patients <50 years %
Tachycardia	71	96
Fatigue	56	84
Weight loss	50	51
Goitre	50	94
Tremor	44	84
Apathy	41	25
Atrial fibrillation	35	2
Anorexia	32	4
Nervousness	31	84
Hyperactive reflexes	28	96
Depression	24	22
Increased sweating	24	95
Polydipsia	21	67
Heat intolerance	15	92
Increased appetite	0	57

Table 1: Incidence of Signs and Symptoms of hyperthyroidism

Thyroid ultrasound

A thyroid ultrasound is usually more sensitive at detecting thyroid nodules. With ultrasound it is easier to diagnose a multinodular goitre which was clinically thought to be a solitary nodule (other nodules not being palpable clinically). This finding has clinical and prognostic significance as a multinodular goitre is said to be less likely to be malignant than a single nodule. It can also differentiate a solid mass from a cystic one. Also, high resolution Ultrasound is better than CT in assessing glandular texture.

CT scan

This examination is particularly useful to determine if there is any compression of the trachea and if there is any retro sternal and retrotracheal extension as sometimes happens in Hashimoto thyroiditis. It will also show the presence of a calcified adenoma or cyst.

Fine needle Biopsy

This is the most cost-effective test in the diagnosis of thyroid nodules, when the nature of the goitre is still in doubt. It is also the best way to assess a nodule for malignancy. Multiple biopsies may be taken under local anaesthetic, but it is to be remembered that with small biopsy specimens, false negative result is a possibility.

Aetiology (see Table 2)

Graves Disease

This is the most common cause of hyperthyroidism, and accounts for up to 75% of all cases.

It is classified as an autoimmune disease caused by an anti TSH receptor antibody which stimulates the gland to synthesize and secrete more thyroxine. There is an increased prevalence of HLA-DR3 which thus appears to occur in a genetically predisposed population, and may be associated with other autoimmune diseases. An infiltrative ophthalmopathy accompanies Graves' disease in 50% of cases.⁴

Toxic Multinodular Goitre

This usually has a more insidious onset, and typically occurs in patients over the age of 50 years who have a longstanding history of goitre. The nodules are usually tender.

Toxic Adenoma

These are usually found in younger individuals especially in iodine deficient areas. There is a single autonomously functioning nodule which is not tender to palpation.

Thyroiditis

Typically is abrupt in onset and usually follows a viral infection. The symptoms may be quite severe and are due to

Cause	Pathophysiology	Gland size	Nodularity
Graves disease thyroid stimulating ab	Increased stimulation of gland	Increased	None
Toxic multinodular goitre	Autonomous hormone production	Increased	Multiple nodules *
Subacute thyroiditis	Leakage of hormone from gland	Increased	None*
Toxic adenoma	Autonomous hormone production	Decreased	Single nodule
Lymphocytic thyroiditis	Leakage of hormone from gland	Increased	None
Iodine-induced (iodide, amiodarone contrast media)	Substance causing stimulation of gland	Increased	Multiple or None
Functioning pituitary adenoma (TSH; trophoblastic tumour hCG)	Increased glandular stimulation	Increased	None
Factitial hyperthyroidism	Exogenous hormone intake	Decreased	None
Metastatic thyroid cancer	Extraglandular hormone production	Decreased	None

*Tender gland

Table 2: Aetiology

hormone leaking from an inflamed gland. Symptoms usually resolve within a few months.

Postpartum thyroiditis can occur in up to 10% of women in the first six months after delivery. The hyperthyroid state may lead to a transient hypothyroid state before resolution.⁵

Tumours

It is indeed quite rare to have a tumour as a cause of hyperthyroidism. Such tumours include: metastatic thyroid cancer, ovarian tumours that produce thyroid hormones and trophoblastic tumours that produce human chorionic gonadotrophin which activate TSH receptors. Pituitary tumours also produce TSH.

Investigation

The initial most significant test to be done in a patient with signs and symptoms of hyperthyroidism is TSH estimation. A very low TSH level is diagnostic of hyperthyroidism. An algorithm for investigating suspected hyperthyroidism is illustrated in figure 1. An elevated TSH warrants the estimation of freeT₄ levels, which if high, indicate secondary hyperthyroidism and necessitate pituitary gland imaging.

Antibody studies

Raised **antimicrosomal** and **antithyroid peroxidase** antibodies are indicative of **Hashimoto's** autoimmune thyroiditis. **Antithyroglobulin** and **antimicrosomal** antibodies are

characteristically elevated in **Graves disease**. Thyroid stimulating antibody levels are also used to monitor the effects of treatment of Graves disease with antithyroid drugs.

Management of hyperthyroidism

Main principles of management:

1. Establish precisely the cause for the hyperthyroidism before starting treatment (Figure 1)
2. Educate your patient and emphasise the need for lifelong monitoring due to possibility of relapse
3. Monitor for cardiovascular complications and osteoporosis

The aim of treatment is to correct the hypermetabolic - state with the least possible side effects including hypothyroidism. The main treatment options are; antithyroid drugs, radioiodine and surgery. The choice depends on the patient's age, size of goitre, co morbidity and patient's desires.

Anti-thyroid drugs

This class of drugs works by interfering with the organification of iodine thus suppressing thyroxine levels. Carbimazole is used locally with a dose of 10-45 mg daily (Methimazole and propylthiouracil are two agents used in the United States) Relapse can occur in up to 50% of patients hence the importance of regular follow-up. A recent RCT⁶ showed that patients with a large goitre, who smoked and had high thyroid-stimulating antibody levels at end of treatment had higher relapse rates.

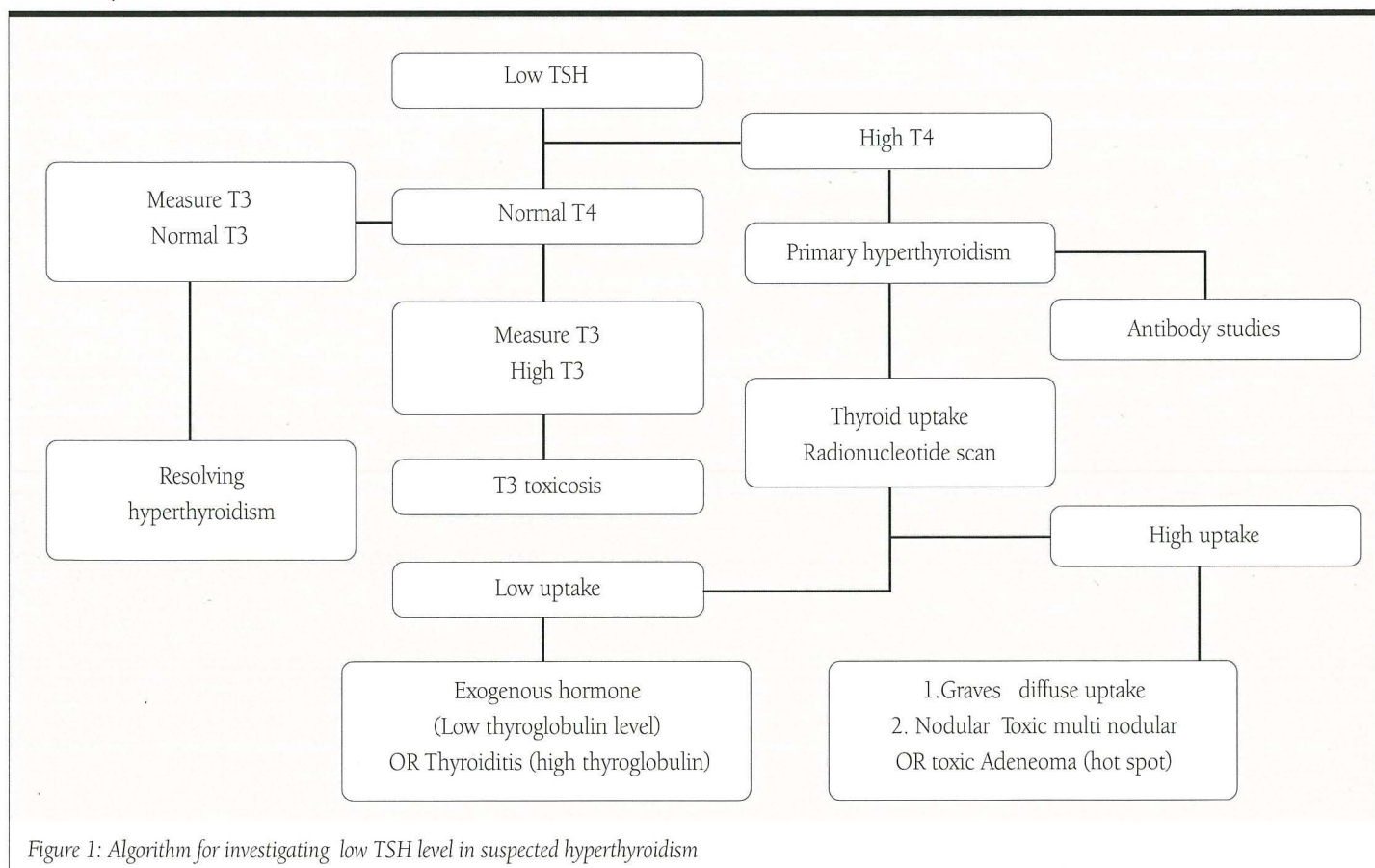


Figure 1: Algorithm for investigating low TSH level in suspected hyperthyroidism

Carbimazole is usually the drug of choice (Propylthiouracil 100-200mg daily is used in pregnancy), with a starting dose of 10mg daily and can be given in combination with Propranolol 10-40 mg 6-8 hourly.⁷ The beta blocker is tapered down over a period of one to two months, and the carbimazole is titrated according to clinical response and monthly free T₄ towards a normal T₃ and T₄ level. It is important to note that the TSH levels may remain very low despite the patient having returned to the normal state with treatment, and should not be used to gauge treatment. After one year of treatment, if the anti-TSH-receptor antibodies are not detectable one can stop the anti-thyroid treatment⁴. The patient should be monitored every three months during the first year as relapse on stopping treatment is common. Once a relapse occurs it is usually recommended that radioactive iodine (¹³¹I) therapy or subtotal/total thyroidectomy be considered. The risk of agranulocytosis is the most serious complication of antithyroid treatment and patients should be warned to stop treatment if they develop sudden fever or sore throat. Arthralgia and polyarticular arthritis may also occur, although to a minor extent.

Surgery

A subtotal thyroidectomy is the most common performed procedure; it preserves some thyroid tissue and hence reduces the risk of hypothyroidism. Total thyroidectomy is reserved for very large goitres and those with very severe symptoms, in whom recurrences are likely. This procedure however carries a high risk of hyperparathyroidism and laryngeal nerve damage⁸.

Radioactive therapy

Radioactive iodine is gradually replacing surgery, and in the United States it is the preferred mode of treatment for Graves' disease and toxic nodular goitre. There is still much debate about the treatment regime of radioiodine. Gland-specific dosage, based on the estimated weight of the thyroid gland, allows a lower dosage to be given and is associated with lower incidence of hypothyroidism, but may have a higher recurrence rate. There is still reluctance to use radiotherapy in women of child bearing age because of the possibility of cancer of thyroid, genetic damage to offspring and leukaemia, however long term study of these patients has failed to support these fears⁹. Patients with toxic adenomas and toxic nodular goitre are more radio resistant and need higher dose regimen to achieve remission. It is important to note that up to 15 % of patients treated with radioiodine, may develop Graves' ophthalmopathy. Ophthalmopathy may be controlled or its incidence reduced with the use of 40 to 80mg of Prednisolone daily¹⁰.

Precautions on radioactivity hazards. Most radioactive sodium iodide is excreted via saliva, urine and faeces within 48 hours of receiving the dose. Close contact with persons should be avoided for up to three days, especially children and pregnant women. It is also recommended to double flush toilet and repeat hand washing for 12 weeks⁹.

Outcome and follow-up

Patients receiving appropriate management have a good prognosis. Some extra-thyroid manifestations of the disease, notably ophthalmopathy, and cardiac complications are resistant to all forms treatment. In view of increased morbidity, patients who have been treated for hyperthyroidism should be screened annually, with special emphasis to atherosclerosis, osteoporosis, diabetes and insidious hypothyroidism¹¹.

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