

# HYPERTHYROIDISM

M. Shuja Tahir, Sohail Aamir

**Abstract:** It is a condition caused by increased function of thyroid gland and effects of increased secretion of thyroid hormones or increase sensitivity. Hyperthyroidism is a condition in which all signs and symptoms are due to increased thyroid hormones. It is essential to confirm the diagnosis by biochemical investigations. Single most important biochemical test is assessment of TSH level. There are three modalities of treatment along with rest and sedation. Drug therapy is given for short term to control thyrotoxicosis prior to definitive treatment with radioiodine ablation or surgery. Radio active iodine I131 destroys thyroid cells and hence reduces functional thyroid tissue. Surgery provides definite treatment for thyrotoxicosis.

**Key words:** Hyperthyroidism, Graves Disease, Radio Iodine, Carbimazole, Thyroidectomy.

It is a condition caused by increased function of thyroid gland and effects of increased secretion of thyroid hormones or increase sensitivity to the hormones leading to pathological increased function of various systems.

Grave's disease (known as Basedow's disease in Europe) is the most common cause of thyrotoxicosis<sup>2</sup>.

Grave's disease is much more common in

females than in males. Female to male ratio is 8:1. Onset of disease is usually between 20-40years.

Patients with Grave's disease have an increased risk of developing Addison's disease, Alopecia areata, Coeliac disease, Diabetes mellitus type I, Myasthenia gravis, Cardiomyopathy & Hypokalemic periodic paralysis.

Hyperthyroidism affects about 2-5% of all females at sometime and with a sex ratio of 5:1 most often between ages of 20-40 years<sup>1</sup>.

Hyperthyroidism is a condition in which all signs and symptoms are due to increased thyroid hormones. While Thyrotoxicosis is a condition in which all symptoms and signs are not explainable on the basis of increased thyroid hormones.

It is essential to confirm the diagnosis by biochemical investigations. Single most important biochemical test is assessment of TSH level. If the TSH level is within the reference range, the diagnosis of hyperthyroidism is ruled out very clearly<sup>1</sup>.

**Article Citation:** Tahir SM, Aamir S. Hyperthyroidism. *Indep Rev Jan-Jun 2017;19(1-6): 13-21.*

**Date received:** 19/04/2017

**Date Accepted:** 13/05/2017

**Correspondence Address:**

**Prof. M. Shuja Tahir**, FRCS(Edin), FCPS Pak (Hon)

Professor of Surgery

Independent Medical College, Faisalabad.

**1. Prof. M. Shuja Tahir**, FRCS(Edin), FCPS Pak (Hon)

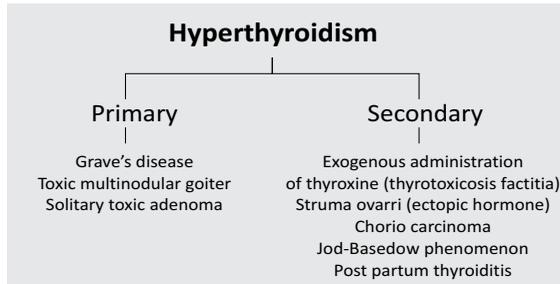
Professor of Surgery

Independent Medical College, Faisalabad.

**2. Sohail Aamir**, FCPS Pak (Hon)

Kingdom of Saudia Arabia.

FT4 & FT3 should be tested in cases of low TSH level assessment. If these are elevated, it is typical case of hyperthyroidism. It may be a case of FT3 thyrotoxicosis, if FT4 level is normal and only FT3 is raised.



**CLINICAL TYPES**

**PRIMARY**

- Grave's disease
- Toxic multinodular goiter
- Solitary toxic adenoma

**SECONDARY**

- Exogenous administration of thyroxine (thyrotoxicosis factitia)
- Struma ovarri (ectopic hormone)
- Chorio carcinoma
- Jod-Basedow phenomenon
- Post partum thyroiditis



Hyperthyroidism with Exophthalmos

**DIFFUSE TOXIC GOITER (GRAVES DISEASE)**

It is an autoimmune disease which usually affects younger females. There is an association with HLA-B8, DW3 and 50% concordance seen in monozygotic twins with

a 5% concordance rate in dizygotic twins<sup>3</sup>.

Yersinia enterocolitica, E.coli and other gram negative bacteria contain TSH binding sites and may be responsible for initiating this autoimmune process.



Malignant Exophthalmos

In these patients there is an increase in IgG antibodies which bind to TSH receptors present in thyroid gland leading to hyper stimulation of thyroid gland because they behave like TSH. These antibodies are called thyroid stimulating immunoglobulins (TSI) and TSH receptor antibodies (TRAB).

This syndrome is also called primary thyrotoxicosis in which there is simultaneous appearances of goiter as well as symptoms of hyperthyroidism. This condition is frequently associated with eye signs.

**TOXIC NODULAR GOITER**

It is also called Plummer's disease<sup>4</sup>. It usually affects middle age to old age group patients. Patients have also a long history of multinodular goiter and develop symptoms of hyperthyroidism later. It is very rarely associated with eye signs although cardiac problems are frequently associated. This syndrome is called secondary thyrotoxicosis.



Hyperthyroidism with Exophthalmos



Exophthalmos &amp; Ophthalmoplegia

## TOXIC NODULE

In this condition there is a single nodule which is hyper active and autonomous and will produce symptoms of thyrotoxicosis. This condition is also called tertiary thyrotoxicosis.

## CLINICAL FEATURES

### SYMPTOMS

- Tiredness
- Heat intolerance
- Emotional Imbalance
- Weight loss despite increased appetite
- Palpitations
- Diarrhea
- Menstrual irregularities
- Insomnia
- Breathlessness (Cardiac failure)

## SIGNS

- Tachycardia
- Moist, sweaty palms
- Lid lag
- Lid retraction
- Exophthalmos
- Goiter with bruit
- Agitation
- Fine resting tremors
- Hyper-reflexia
- Fine hair
- Osteoporosis in chronic thyrotoxicosis
- Onycholysis
- Finger clubbing & swelling of fingers (acropathy)

## EYE SIGNS

They can be unilateral or bilateral. They are commonly associated with primary hyperthyroidism or Graves disease. Graves ophthalmopathy is an autoimmune disease.

### Lid Retraction

Spasm of upper eye lid and retraction results in widening of palpebral fissure (Stellwags Sign) so sclera is visible above upper limbus. Lid spasm and retraction occur because levator palpebrae superioris muscle is partially innervated by sympathetic fibers. As we know thyroid hormone increase the sensitivity of catecholamine receptors, so the increased circulating thyroid hormone in these patients causes spasm of the muscle.

### External Ophthalmoplegia

Present in 40% of patients having hyperthyroidism. There is weakness of extra ocular muscles especially elevators (inferior oblique) which results in diplopia. Cause of ophthalmoplegia is not known. There are theories regarding its pathogenesis. Some say that thyroid stimulating antibodies while circulating in blood cross react with eye

muscle antigens. Others say that complexes of thyroglobulin and anti-thyroglobulin bind to extra ocular muscles.

### Exophthalmos

It is protrusion of eye ball. It can be appreciated clinically and can be measured with optimeter. Exophthalmos is due to retro bulbar infiltration of lymphocytes and mucopolysaccharides. Cause is still not known but pituitary exophthalmos producing substances may be the causative factor, some say it is due to TSA<sub>b</sub> which cross react with eye muscle antigens and will lead to immune mediated infiltration of round cells and fluid in retro bulbar space.

### Congestion, Oedema and Corneal Ulcers

This stage develops if condition remains untreated because of ophthalmic veins compression caused by retro bulbar infiltration of round cells and fluid. When papilloedema and corneal ulceration are severe and progressive then this condition is called malignant exophthalmos and eye may be at stake.

### CARDIAC SIGNS

Cardiac problems are usually associated with secondary thyrotoxicosis or toxic multi nodular goiter and are common in older age group because of their compromised heart condition. Stages of development of thyroid cardiac problems are:

- Sinus tachycardia
- Multiple extra systole
- Paroxysmal atrial tachycardia
- Paroxysmal atrial fibrillation
- Persistent atrial fibrillation

### MYOPATHY

Weakness of proximal limb muscles is a common finding in patients with hyper-

thyroidism although severe muscle weakness like myasthenia gravis is rare. Recovery is good as hyperthyroidism is controlled.

### PRETIBIAL MYXOEDEMA

It is thickening of skin by mucin like deposits because of immune mediated process conducted by TSA<sub>b</sub>. It is usually present in patients having primary hyperthyroidism with exophthalmos usually bilateral.

At earlier stages there is shiny red plaque thickened skin with coarse hair which may be cyanotic when exposed to cold. In advanced stages skin of whole leg below knee is involved with clubbing of fingers and toes then the condition is called thyroid acropathy.

### DIAGNOSIS

Diagnosis is mainly clinical. Anyhow confirmation of diagnosis and assessment of the status of hyperthyroidism can be performed by various investigations.

CT scanning and ultrasound can also be used.

### TREATMENT

There are three modalities of treatment along;

#### Anemia

Decreased granulocytes  
Increased serum ANA / anti double stranded DNA antibodies. There is no evidence of lupus Erythematosus or other collagen disease.

### IMAGING

MRI of orbits is the imaging method of choice to visualize ophthalmopathy affecting the extra ocular muscles.

CT scanning and ultrasound can be used.

**COMPLICATIONS**

Cardiac complications of thyrotoxicosis include Atrial Fibrillation with a ventricular response which is difficult to control.

Episodes of periodic paralysis induced by heavy exercise, carbohydrate ingestion, and accompanied by hypokalemia may complicate thyrotoxicosis in Asian or Native American men.

Hypercalcemia, osteoporosis & nephrocalcinosis may occur.

Decreased libido, impotence, decreased sperm count & gynaecomastia may be noted in men with hyperthyroidism.

**TREATMENT**

There are three modalities of treatment along with rest and sedation. These are;

- Radio-iodine ablation
- Surgery
- Medical treatment

**MEDICAL TREATMENT (DRUG THERAPY)**

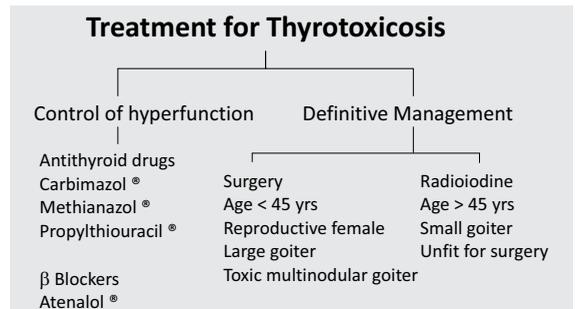
Following groups of drugs are used to treat hyperthyroidism:

- i. Anti-thyroid drugs
  - Carbimazole
  - Methimazole
  - Propylthiouracil
- ii Beta blockers
  - Propranolol
  - Nadolol
- iii Iodides

**ANTI THYROID DRUGS  
CARBIMAZOLE (NEOMERCAZOLE)**

It is available in 5 mg tablets. It blocks oxidation of iodine and organification of iodine with tyrosine and prevents coupling of mono iodotyrosine (MIT) and di-iodotyrosine (DIT).

Initially start 30-40 mg per day in divided doses. When patient is euthyroid, then change to maintenance dose of 5 mg two to three times daily for 12 to 18 months.



TSH  
T3/T4  
Antibodies  
Ultrasound  
FNA for  
Solitary nodule  
Hypercalcemia  
Increased alkaline phosphatase  
Anemia  
Decreased granulocytes  
Serum ANA / anti double stranded DNA antibodies are also usually increased without any evidence of lupus Erythematosus or other collagen vascular disease.

**Investigations**

```

            graph TD
                Root[Investigations] --> TSH[TSH]
                TSH --> Low[Low]
                TSH --> Normal[Normal]
                Low --> T3T4[T3/T4]
                Low --> Antibodies[Thyroid Antibodies  
(TRAB, ANTI THYROGLOBULIN Ab)]
            
```

## PROPYLTHIOURACIL

Available as 100 mg tablets. Its dose is 100 - 300 mg TDS. Mode of action is same as that of carbimazole and in addition to that it prevents peripheral conversion of T4 into T3. It can be given safely in pregnancy in reduced doses as it does not cross placental barrier.

## DURATION

Drug therapy is given for short term to control thyrotoxicosis prior to definitive treatment with radioiodine ablation or surgery.

Drug therapy is given for longer term in Grave's disease with objective of achieving remission.

## TITRATION REGIMEN

A reducing dose of the drug is given with dose adjustments made according to serum thyroxine levels checked every 4-6 weeks.

When the patient is established on maintenance dose the follow up T4 estimations are carried on every three months.

## SIDE EFFECTS OF ANTI THYROID DRUGS

- Agranulocytosis in less than one year of treatment
- Peripheral neuritis
- Myalgias
- Lymphadenopathy
- Psychosis
- Liver dysfunction
- Skin rash
- Arthralgia

Aplastic Anemia may follow after prolong use of antithyroid drugs. If sides effects occur, then methimazole (Tapazole) is given which is 10 times more potent than carbimazole and propyl-thiouracil.

## BETA BLOCKERS

Propranolol or nadolol are used in addition to anti-thyroid drugs as they decrease sensitivity of catecholamine receptors to thyroid hormones hence these help in improving constitutional symptoms like tremors, tachycardia etc. Dose of propranolol is 40 mg x TDS and of nadolol is 160 mg once a day.

## IODIDES

These salts increase colloid storage of gland and hence decrease vascularity of gland. These are given in last few days to the patient before surgery in addition to antithyroid drugs. These are available as Lugol's iodine and potassium iodide tablets.

Lugol iodine contains potassium iodide 10g/100 ml and iodine 5g/100ml . Its dose is 5 drops 8 hourly in milk.

Potassium iodide tablets are used as an alteration to lugol iodine solution. There dose is 100 mg x TDS.

## BLOCK & REPLACE REGIMEN

Carbimazole® 40mgperdayorPropylthiouricil 30mg per day are continuously given and iatrogenic hypothyroidism is prevented by addition of thyroxine 100-150 ug per day until the patient is euthyroid. Continuous mon-itoring by thyroid function test is carried on during this regimen.

## RADIO IODINE ABLATION

Radio active iodine I131 destroys thyroid cells and hence reduces functional thyroid tissue. Its dose is 5-15 mei.

For diffuse toxic goiter it is 7-9 mei and for toxic nodular goiter it is 12-15 mei. Patient is made euthyroid before radio iodine

administration and then given 5-15 mei of I131 orally. About 75% of patients respond to this dose in 3 months. Rest of the 25% of patient with persistent thyrotoxicosis require double of initial dose.

Patients are given anti thyroid drugs after an initial dose of I131 in first 1-2 weeks to counter the effect of thyroid hormone release which may cause thyroid crisis.

### SIDE EFFECT

- Leukemia
- Radiation thyroiditis
- Thyroid carcinoma
- Genetic mutation
- Fetal damage if given during pregnancy

### ABSOLUTE INDICATIONS

Recurrence after sub total thyroidectomy  
Old age patient with poor life prognosis

### ADVANTAGES

No surgery required  
No prolonged treatment required

### CONTRAINDICATIONS

Pregnancy  
Lactation  
(pregnancy should not be planned for 4 months after the treatment)

### DISADVANTAGES

Essential follow up  
High incidence of thyroid insufficiency

### SURGERY

Surgery provides definite treatment for thyrotoxicosis, if antithyroid drugs have failed to produce a remission or thyrotoxicosis has relapsed or radioiodine ablation is contra-indicated.

Most appropriate candidates for surgery are;  
Young female  
Children  
Large goiters  
Patients with contraindication to radio ablation

Options are lobectomy in patient having toxic nodule.

Sub total thyroidectomy; In patient having diffuse toxic goiter and toxic multinodular goiter.

### INDICATIONS

Diffuse toxic goiter in patient < 45 years  
Toxic multinodular goiter  
Toxic nodule

### ADVANTAGES

Rapid cure

### DISADVANTAGES

- Recurrence of thyrotoxicosis in up to 5% cases
- Post operative thyroid insufficiency in up to 25-40% cases
- Long term follow up essential
- Para thyroid insufficiency in <0.5% of cases

### PREPARATION OF PATIENT FOR SURGERY

#### AIMS

- To make the patient euthyroid which restores nutritional status of the patient
  - To decrease bleeding during surgery
  - To improve response of patient to surgery
- Preparation is done usually on out patient basis. Hospital admission is rarely required for the patients in which hyperthyroidism remains uncontrolled.

Patient is given anti-thyroid drugs, carbimazole 30-40 mg per day in divided doses for 4-6 weeks before surgery. Beta blockers like propranolol are also given in 40 mg thrice daily doses. Addition of beta blockers helps in rapid preparation of the patient for surgery within two weeks time. Iodine may be given 10-14 days prior to surgery but its role is contro-versial.

The last dose of carbimazole is given on the evening before surgery while the morning dose is omitted.

Beta blockers are continued up to 7th to 14th post operative day. It is important to note that addition of iodine in the last 10 days before operation gives an additional safety measure in case the morning dose of beta blockers is mistakenly omitted on the day of surgery.

**CHOICE OF TREATMENT FOR DIFFERENT THYROID CONDITIONS DIFFUSE TOXIC GOITER**

Age > 45 years	Age < 45 years
Radio iodine ablation	Surgery for large goiter
	Antithyroid drugs from small goiter
	Radioiodine ablation in cases where family is complete

**TOXIC MULTI NODULAR GOITER**

Surgery is the only option after making the patient euthyroid.

**TOXIC NODULE**

Age > 45 years	Age < 45 years
Radio iodine ablation	Surgery
Surgery if patient is fit	

**TREATMENT OF OCULAR PROBLEMS OF GRAVES DISEASE:**

The patient is made euthyroid. Regular monitoring is continued when anti-thyroid drugs are being given as hyperthyroidism may enhance exophthalmos.

Patient is advised to stop smoking.

The patient is kept propped up while sleeping. Diuretics are also given. It will decrease retro bulbar edema and will alleviate compression of ophthalmic veins.

The eyes are protected from dust and light either by some ointment, methylcellulose eye drops or by lateral tarsorrhaphy.

Beta blocker eye drops are given (Guanethidine eye drops). It improves spasm and retraction of lids.

For acute, progressive exophthalmos, intravenous methylprednisolone, begun promptly, is superior to oral prednisolone, possibly due to improved compliance. Methylprednisolone is given intravenously, 500mg weekly for 6 weeks, then 250mg weekly for 6 weeks. If oral prednisolone is chosen for treatment, it must be given promptly in daily doses of 40-60mg per day orally, with doses reduction over several weeks. Higher initial prednisolone doses of 80-120mg per day are used when there is optic nerve compression. Prednisolone alleviates eye symptoms in 64% of nonsmokers, but only 14% of the smokers respond well.

Progressive active exophthalmos may be treated with retrobulbar radiation therapy using a supervoltage linear accelerator (4-6MeV) to deliver 20Gy over 2 weeks to the extra ocular muscles, avoiding the cornea

and lens.

If exophthalmos persists despite medical treatment then either retro bulbar radiation or surgical decompression of eye ball is performed.

There are chances of cataract formation with retro bulbar radiation.

### DIFFERENTIAL DIAGNOSIS

- Anxiety neurosis
- Pheochromocytoma
- Carcinoid syndrome
- Hypocalcemia
- Paroxysmal atrial tachycardia

Hyperthyroidism may be confused with anxiety neurosis or mania, but in the latter, the thyroid is not enlarged & thyroid function tests are usually normal.

Pheochromocytoma is often associated with hypermetabolism tachycardia, weight loss and profuse sweating.

Cardiac disease (e.g. arterial fibrillation, angina) refractory to treatment suggest the possibility of underlying (apathetic) hyperthyroidism.

Other causes of ophthalmoplegia (e.g. myasthenia gravis) & exophthalmos (e.g. orbital tumour, pseudotumour) must be considered.

Thyrotoxicosis must also be considered in differential diagnosis of muscle weakness and

osteoporosis. Diabetes mellitus and Addison disease may coexist with thyrotoxicosis.

### HYPERTHYROIDISM DUE TO RARE CAUSES

Viral (De Quervain thyroiditis) can cause hyperthyroidism in earlier stages

### THYROTOXICOSIS FACTITIA

Thyrotoxicosis factitia refers to a condition of thyrotoxicosis caused by the ingestion of exogenous thyroid hormone. It can be the result of mistaken ingestion of excess drug, such as levothyroxine, or as a symptom of Munchausen syndrome. It is an uncommon form of hyperthyroidism.

### JOD BASEDOWS THYROTOXICOSIS:

In this case large doses of iodine given in endemic goiter may produce hyperthyroidism because of activity of thyroid tissue to iodine.

### CARCINOMA OF THYROID

It can sometimes produce hyperthyroidism. Neonate thyrotoxicosis can occur in babies born to hyperthyroid mothers or mothers who are euthyroid but have previous history of thyrotoxicosis. In these patients thyroxine antibodies cross placental barrier and produce hyperthyroidism in new born. This condition subsides in 3-4 months period as thyroxine antibodies level falls in the serum.

### REFERENCES

1. British Thyroid Association. UK Guidelines for thyroid tests. July 2006: 32-38. [www.british-thyroid-association.org](http://www.british-thyroid-association.org)
2. Paul A. Fitzgerald. Endocrinology CMTD 2007: 1158-1159.