

## **Hyperthyroidism – clinical features and treatment**

### **1. The causes of hyperthyroidism**

The thyroid is a gland in the neck that produces two thyroid hormones, thyroxine (T4) and tri-iodothyronine (T3). Thyroxine is inactive and is converted by the tissues and organs that need it into tri-iodothyronine. The role of thyroid hormones, put simply, is to regulate the metabolism of virtually all cells in the body. In health, the production of these thyroid hormones is tightly regulated by the secretion of thyroid stimulating hormone (TSH; also known as thyrotropin) from the pituitary gland in the brain. When the thyroid gland becomes affected by disease, sometimes the production or release of thyroxine and tri-iodothyronine can be abnormally high, leading to increased levels in the blood; a state of thyroid overactivity known as hyperthyroidism or thyrotoxicosis. If this happens, the body's metabolism speeds up and this can be manifest by changes in various, and seemingly unrelated tissues, that are listed below. In this state of hyperthyroidism, a blood test will show an elevated amount of these thyroid hormones circulating. Conversely, the TSH level in the blood almost always becomes suppressed, because the pituitary gland senses ('sees') the abnormally high levels of thyroid hormones, which are more than is needed by the brain.

The prevalence of hyperthyroidism is about 1% and it is about six times more common in women. There are two main causes of hyperthyroidism in the UK:

- 1). Autoimmunity causing stimulation of the thyroid gland
- 2). Overproduction of hormones by benign tumours in the thyroid gland.

1). In autoimmune thyroid overactivity, the thyroid cells are stimulated by an abnormal antibody which is specifically targeted at the TSH-receptor on the thyroid gland causing stimulation of the thyroid to produce excess hormones. This also causes the thyroid cells to grow, and together with immune cells congregating in the gland, this leads to thyroid enlargement, called goitre.

An early description of this form of autoimmune thyroid disease was made by an Irish physician called Robert Graves, so it is often termed Graves' disease. Graves' disease is almost always accompanied by the presence of the TSH-receptor autoantibodies in the blood and very frequently by thyroid peroxidase (TPO) autoantibodies which may both be a useful tool for diagnosis. In addition, about a third of people with Graves' disease develop a variety of eye problems including a staring appearance, grittiness and soreness, protruding eyeballs, and (rarely) double vision or sight problems. This is termed "thyroid eye disease" or "Graves' ophthalmopathy". Cigarette smoking increases the risk of developing thyroid eye disease in patients with Graves' disease.

2). The other common cause of thyroid overactivity is that the thyroid develops one or more benign tumours (technically follicular adenomas but often simply called “nodules”) that secrete excess thyroid hormone in an unregulated manner. This nodular hyperthyroidism becomes commoner with advancing age and is termed “solitary toxic nodule” or “toxic multinodular goitre”, depending on the number of nodules.

Together these two types of hyperthyroidism account for well over 90% of all cases. Rarer causes include inflammatory conditions of the thyroid called thyroiditis, which sometimes is the result of pregnancy, viruses or drugs such as amiodarone or interferon. All the types of hyperthyroidism just mentioned are usually classified as *primary*, meaning that they result from an excess stimulation or release of thyroid hormone from the thyroid gland. Very rarely, there may be secondary thyroid overactivity as a result of a pituitary problem where the pituitary gland manufactures an excess amount of TSH (thyroid stimulating hormone). This leads to thyroid overactivity with normal or high blood TSH. More commonly blood tests that have the same pattern as primary thyroid overactivity can result from taking an excess of thyroid hormone tablets, such as levothyroxine.

## **2. The symptoms and signs of hyperthyroidism**

Common complaints include fatigue, heat intolerance, sweating, weight loss despite good appetite, shakiness, inappropriate anxiety, palpitations of the heart, shortness of breath, tetchiness and agitation, poor sleep, thirst, nausea and increased frequency of defecation. The elderly may complain predominantly of heart problems with a fast or irregular heart beat, breathlessness and ankle swelling, whereas children tend to hyperactivity, with a short attention span. Signs include shaky and hot hands, fast or irregular heart beat, inability to sit still, flushing of the face and upper trunk, fast tendon reflexes, an enlarged thyroid gland and prominent or bulging eyes. Nowadays patients often are diagnosed at an early stage of disease, owing to increased awareness and improved biochemical testing. Therefore some patients have relatively few of the classical signs or symptoms. In addition, none of the symptoms or signs just listed is sufficiently sensitive or specific for the diagnosis of hyperthyroidism, even when combined together. Thus, it may take three to six months to diagnose hyperthyroidism, during this time the person can feel very unwell. It is not uncommon for people to worry that they have cancer, because of the associated weight loss.

### **3. Treatment of hyperthyroidism**

#### *Graves' disease and nodular thyrotoxicosis*

##### Betablockers

Betablockers are a group of drugs that tend to improve some of the symptoms and manifestations of hyperthyroidism. In particular, they can improve palpitations, slow the heart down and improve tremor. They have no effect on curing the thyroid overactivity, but do make many people feel better. Betablockers should not be taken if the patient has asthma or a wheezy chest.

##### Antithyroid drugs

Carbimazole (Neomercazole) and propylthiouracil are antithyroid drugs that are effective in reducing the production of thyroid hormones in the majority of people with hyperthyroidism. In people with Graves' disease, treatment with one of these drugs for between 6 months and 2 years results in a long-term remission in around half of patients, once the drug is stopped.

Both drugs have the common side effects of rash and joint pains, and more rarely (less than 1 in 500 cases) a serious reduction in the circulating white blood cells (agranulocytosis) may occur during treatment. The dosage of these antithyroid drugs can either be adjusted every 6 to 8 weeks according to thyroid hormone levels in the blood, to keep the person's thyroid hormone levels in the normal range (titrated dose regimen) or kept at a fixed, higher dose and levothyroxine replacement added to maintain normal thyroid hormone levels (block and replace regimen). In nodular hyperthyroidism (solitary toxic nodule or toxic multinodular goitre), antithyroid drugs do not result in cure, just a temporary reduction in thyroid hormone levels. A more permanent solution is often sought, called a definitive treatment.

##### Radioiodine

Radioiodine is a radioactive isotope of iodine ( $^{131}\text{I}$ ) that is taken up and concentrated selectively by the thyroid gland. In most people, this small dose of radioactivity is sufficient to gradually destroy the thyroid tissue, over 6 weeks to 6 months following a single dose. Patients with Graves' disease have a high rate of permanent thyroid underactivity following radioiodine (about 80%), whereas patients with nodular thyroid overactivity tend to preserve their thyroid function better, with only around half eventually becoming underactive. Patients are monitored for underactivity following the dose and promptly treated with thyroxine, should this develop. The common outcome of thyroid underactivity is an accepted consequence of radioiodine therapy because hyperthyroidism is a serious condition whereas replacement treatment with levothyroxine is simple and has no side effects at the correct dose.

Radioiodine is a safe treatment for thyroid overactivity, with no overall excess of cancers in many hundreds of thousands of patient years of follow up (JAMA 1998; 280: 347-355; Lancet 1999; 353: 2111-5). Patients with ophthalmopathy require careful evaluation, as radioiodine may worsen

thyroid eye disease: this can be prevented by a short course of steroid tablets. There is no damage to fertility or to hair growth, but women are advised not to become pregnant for 6 months following a dose, as the baby's thyroid could be damaged. Men should avoid fathering a child within 4 months of treatment. Following a standard dose of radioiodine, other precautions are necessary to minimise radiation exposure of others but these restrictions are usually easily accommodated by the patient. Radioiodine may trigger airport security alarms up to eight weeks following a dose and patients should carry a letter about the treatment if they travel in this period. Radioiodine is the most cost effective and certain treatment for thyroid overactivity and about 10,000 doses annually are given in the UK.

### Thyroid surgery

Surgery to remove most or all of the thyroid gland (subtotal or total thyroidectomy) is another way of definitively treating thyroid overactivity. This is a straightforward operation when carried out by an experienced thyroid surgeon, with a low risk of complications. Hypothyroidism is a recognised side effect of surgery for which levothyroxine replacement will be needed, lifelong. Thyroidectomy is a good treatment option for people with a large goitre and for those with thyroid eye disease. Prior to thyroid surgery, thyroid overactivity needs to be controlled, usually with antithyroid drugs to make an anaesthetic safe. This is because an anaesthetic in a hyperthyroid person has a high risk of precipitating a dangerous hyperthyroid crisis or "thyrotoxic storm".

### *Treatment of thyroiditis*

Many forms of thyroiditis are 'self-limiting', meaning that the overactivity recovers spontaneously and no treatment may be required. If the person has severe symptoms of thyrotoxicosis, betablockers are helpful. However, in some cases thyroiditis can be painful or prolonged and anti-inflammatory tablets or steroids may be helpful. Furthermore, in some cases a period of thyroid underactivity may follow the thyrotoxicosis, and this may require levothyroxine treatment, if causing severe symptoms.

### *Subclinical hyperthyroidism*

In subclinical hyperthyroidism, the TSH is suppressed but the free thyroid hormone levels are normal. Endocrinologists regard this condition as a precursor of overt or clinical hyperthyroidism but there is some debate over whether this mildest of degree of hyperthyroidism should be treated (JAMA 2004; 291: 228-238, J Clin Endocrinol Metab. 2007 ;92:3-9.). Further research is being conducted in this area. At present treatment is a matter for individual clinical evaluation and discussion between patient and doctor, although there is a consensus that treatment may be worthwhile in the elderly, particularly if the heart rhythm becomes abnormal or there is thinning of the bones or low-impact bone fractures.