

Hypothyroidism – clinical features and treatment

1. The causes of hypothyroidism

The thyroid is a gland in the neck which makes 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. When there is too little thyroid hormone (hypothyroidism) the body's metabolism slows down and this is manifested by changes in various tissues that are listed below. Around 80% of tri-iodothyronine in the body is derived from conversion of thyroxine in the tissues (a process mediated by deiodinase enzymes), the remainder coming directly from the thyroid gland. Most (>99%) of the thyroid hormone in the blood is bound to proteins and is not available to cells. The free fraction of T4 and T3 in the blood is therefore a more useful measure of thyroid hormone levels than the total amount of these hormones. This is what is meant by free T4 (FT4) and free tri-iodothyronine (FT3).

The prevalence of hypothyroidism is about 2% and this is ten times more common in women. There are two main causes of hypothyroidism in the UK, namely autoimmunity and as a side effect of treatment for an overactive thyroid or for thyroid cancer. In autoimmune thyroid diseases, the thyroid cells are destroyed by white blood cells (lymphocytes) which attack the thyroid. Autoimmune thyroid disease is usually accompanied by the presence of thyroid peroxidase (TPO) autoantibodies which can be detected in the blood and are therefore a useful tool for diagnosis. In patients who have an overactive thyroid or thyroid cancer, treatment may consist of surgery or radioiodine, both of which destroy the diseased gland but inevitably result in a significant proportion of patients developing hypothyroidism.

Together these two types of hypothyroidism account for well over 90% of all cases. Rarer causes include inflammatory responses in the thyroid (sometimes as the result of viruses or drugs such as amiodarone or lithium), abnormal thyroid development in the foetus and genetic defects in thyroid function (leading to congenital hypothyroidism which should usually be picked up during neonatal screening). Iodine deficiency is still a common cause of hypothyroidism in some parts of the world but is very rarely encountered in the UK. All the types of hypothyroidism just mentioned are usually classified as *primary*, meaning that they result from direct impairment of the thyroid gland's function.

Impaired thyroid function may also occur as a result of pituitary disease, because the pituitary manufactures TSH (thyroid stimulating hormone) which is the most important internal factor controlling thyroid function. If the pituitary is damaged and cannot make TSH, the thyroid stops working. Although uncommon, such *secondary* hypothyroidism is important as the normal blood test used to test for the presence of primary hypothyroidism (namely the TSH level) can be misleading. Such patients usually have other clinical features suggestive of pituitary disease, so a careful history and clinical examination will point to the correct blood tests that need to be undertaken if hypothyroidism is suspected.

2. The symptoms and signs of hypothyroidism

Common complaints include fatigue and lethargy, cold sensitivity, dry skin and lifeless hair, impaired concentration and memory, increased weight with poor appetite and constipation. Patients may also fairly often experience a hoarse voice, tingling of the hands (carpal tunnel syndrome), heavy and, later, absent periods, deafness and joint aches. In childhood there may be delayed development and in the adolescent precocious puberty. The elderly may develop memory disturbance, an impaired mental state or depression, and in rare cases coma can occur, resulting in death if left untreated. Signs include slow movements, 'myxoedema facies' in which the face looks puffy due to the accumulation of subcutaneous fluid, cool dry skin, slow pulse rate, thinning of the hair including the eyebrows, slow tendon reflex relaxation time, slow pulse rate and hoarse voice. The thyroid may be enlarged (causing a goitre) in some patients due to accumulation of lymphocytes (Hashimoto's thyroiditis), but in others the thyroid is destroyed by the time of diagnosis and there is no goitre.

Nowadays patients often are diagnosed at an early stage of disease, due to increased awareness and improved biochemical testing. Therefore many patients have relatively few of the classical signs or symptoms just listed. In addition, none of the symptoms or signs is sufficiently sensitive or specific for the diagnosis of hypothyroidism, even when combined together.

3. Treatment of hypothyroidism

Thyroxine

Thyroxine (or levothyroxine) is the current standard thyroid hormone replacement recommended in the British National Formulary (BNF). Patients in the UK who require thyroxine can obtain an exemption certificate, which means that they do not

have to pay for prescriptions of this drug. This is the standard treatment for thyroid hormone deficiency. It has a half life of 7 days and is readily converted into triiodothyronine (by a process called peripheral deiodination) in the body's tissues. This same process occurs with the thyroxine secreted by the thyroid.

Goal of treatment with thyroxine

The goal of treatment in primary hypothyroidism is to reverse the symptoms of hypothyroidism by normalising the blood TSH level. The most recent UK guidelines, published by the Association of Clinical Biochemists and the British Thyroid Association (BTA) in 2005, state 'The aim of treatment should be to restore and maintain the TSH level within the reference range' (<http://www.acb.org.uk/docs/TFTguidelinefinal.pdf>).

The TSH blood test is successful in establishing the correct dosage of thyroxine because there is a feedback loop between thyroid hormone in the blood and the pituitary. When thyroid hormone levels are low, TSH levels rise, and conversely when thyroid hormone levels are high, the TSH levels fall. The pituitary is very sensitive to changes in circulating thyroid hormone levels and the amount of TSH it secretes is therefore a useful yardstick to measure how much thyroid hormone the whole body is exposed to.

Prolonged periods of overtreatment with thyroid hormone (associated with a reduction of TSH levels below the reference range) increase the risk of developing atrial fibrillation (an irregular heart rhythm associated with a risk of stroke) and bone thinning (summarised in JAMA 2004; 291; 228-238).

Measurement of serum T4 or T3 levels on their own are not recommended for monitoring thyroid hormone replacement in primary hypothyroidism, as the levels may change through the day after ingestion of a tablet and the levels do not reflect the tissue response to thyroid hormone in the way TSH does. For instance, if a patient omits thyroxine tablets for a few weeks the TSH levels will rise, but the FT4 level will be normal if the patient then remembers to take thyroxine for a day or two before attending clinic.

Subclinical hypothyroidism

In subclinical hypothyroidism, the TSH is elevated but the free thyroid hormone levels are normal. Endocrinologists regard this condition as a precursor of overt or clinical hypothyroidism but there has been considerable debate over whether even this

mildest of degrees of hypothyroidism can be associated with symptoms and whether it should be treated (JAMA 2004; 291: 228-238, J Clin Endocrinol Metab 2005; 90: 581-585). 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 is usually worthwhile if repeated TSH levels exceed 10mU/L.

Use of tri-iodothyronine

Around 80% of circulating T3 arises from the peripheral tissues by deiodination of T4 and only around 20% is directly secreted by the thyroid gland. Thyroxine treatment in hypothyroid individuals is predicated on the assumption that this 'missing' 20% of T3 can be compensated for by increased peripheral deiodination.

There have been recent trials of tri-iodothyronine replacement in combination with replacement of thyroxine. However T3 given as a liothyronine (or tertroxin) tablet does not reflect a physiologically relevant replacement. Firstly, its half life is 24 hours and administration results in undesirable, non-physiological peaks of serum T3. Secondly, a molar ratio of 14:1 T4:T3, delivering around 100mcg T4 and 6mcg T3 per day, would be optimal for an average adult patient. Liothyronine tablets are 20mcg in size, making any approach to mimic normal T3 replacement extremely difficult with standard sized tablets, especially in those who still have a degree of thyroid remnant function.

Despite initially promising results in a small trial, the benefits of T3 and T4 combination treatment in patients with hypothyroidism have not been borne out by several large and more prolonged trials. Data from 11 independent randomised control trials (1216 patients) were pooled and reviewed in J Clin Endocrinol Metab 2006; 91: 2592-2599).

There was no overall objective evidence of benefit in terms of symptom scores (body weight, depression, fatigue, quality of life) or other physiological markers (serum cholesterol, triglyceride levels, low or high density lipoprotein. At present, combination treatment is not recommended by endocrinologists. Future work is needed to determine whether any benefits might occur with sustained release T3 preparations which are not yet developed for use.

Armour thyroid extract

Armour thyroid extract is desiccated animal thyroid extract which was superseded by synthetic thyroxine in the 1960s. It must be obtained from the USA. Although not normally prescribed in the UK, because it is not licensed for use, it can be given through the NHS if specific arrangements are made on a named patient basis. According to the Medicine and Healthcare Products Regulatory Agency, it is the decision of individual NHS Trusts as to whether an unlicensed product like Armour is made available on a NHS or private prescription.

Armour thyroid extract is not recommended by endocrinologists as standard thyroid hormone replacement treatment, as the amount of thyroid hormone is more variable between batches than it is in thyroxine tablets. Furthermore, the ratio of T3 to T4 in Armour thyroid extract tablets is higher than is normally secreted by human thyroid tissue, resulting in potentially harmful levels of T3 (one grain, about 60 mg, of desiccated thyroid extract contains about 38mcg of T4 and 9mcg of T3). The position of the BTA is set out in a statement (<http://www.british-thyroid-association.org/armour.htm>). Although some patients wish to take Armour, for instance, because they perceive it to be 'natural' rather than 'synthetic', there have been no scientific studies that compare it to thyroxine, and there is a theoretical reason based on the ratio of T3 to T4 to believe it could have adverse effects.

Thyroid hormone treatment in euthyroid individuals

Only one prospective study has been conducted to assess the possible benefit of thyroxine treatment in euthyroid individuals (Brit Med J 2001; 323: 891-895). In this controlled trial there was no effect of thyroxine. There are also strong theoretical reasons to believe that such treatment is futile. The full position of the BTA is summarised in a joint statement with the Society for Endocrinology (http://www.british-thyroid-association.org/thyroid_statement.pdf).