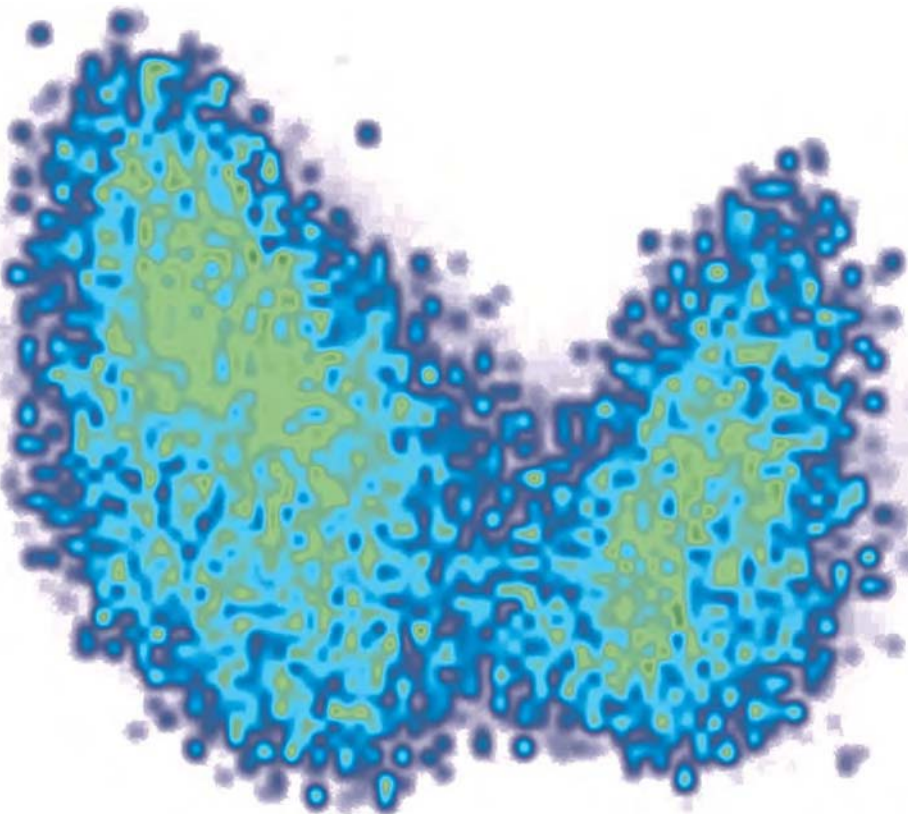


Fast Facts



# Fast Facts: Thyroid Disorders

Gilbert H Daniels and Colin M Dayan



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# Fast Facts: Thyroid Disorders



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## **Declaration of Independence**

This book is as balanced and as practical as we can make it.  
Ideas for improvement are always welcome:  
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## Glossary

**ACTH:** adrenocorticotrophic hormone; a hormone secreted by the anterior pituitary gland that stimulates secretion of glucocorticoids by the adrenal cortex

**Amiodarone-induced thyrotoxicosis:** type 1 is induced by the high iodine content of amiodarone, and may be due to Graves' disease or toxic nodular goiter; type 2 is a form of destructive thyroiditis resulting from the toxic effects of amiodarone and/or its metabolites

**ANCA:** anti-neutrophil cytoplasmic antibodies

**Athyrosis:** congenital absence of the thyroid gland

**Bruit:** an intermittent, harsh or musical auscultatory sound

**CEA:** carcinoembryonic antigen (a tumor marker)

**Deiodinase:** several related enzymes responsible for conversion of T4 to active T3 (types 1 and 2) or to the inactive form of T3, reverse T3 (type 3)

**Euthyroidism:** normal function of the thyroid, in which the proper amount of hormone is secreted with correct constitution

**Familial dysalbuminemic hyperthyroxinemia:** a genetic disorder characterized by elevations in serum total thyroxine and (in some assays) free T4, caused by an abnormal serum albumin that has increased affinity for thyroxine

**Follicular thyroid carcinoma:** a well-differentiated thyroid carcinoma derived from follicular cells

**G-CSF:** granulocyte colony-stimulating factor

**Goiter:** an enlargement of the thyroid

**Graves' disease:** an autoimmune condition in which anti-TSH-receptor antibodies stimulate the thyroid and produce hyperthyroidism

**Hashimoto's disease:** a type of chronic autoimmune thyroiditis that may cause primary hypothyroidism

**HCG:** human chorionic gonadotropin, a hormone produced during pregnancy and in pregnancy-related states, which can mimic the action of thyroid-stimulating hormone on the thyroid

**Hot nodule:** an autonomously functioning thyroid adenoma that is defined by its enhanced ability to accumulate radio-iodine

**Hydatidiform mole:** an uncommon benign tumor that develops from placental tissue early in a pregnancy in which the embryo has failed to develop normally and secretes high levels of HCG

**Hyperemesis gravidarum:** excessive vomiting in early pregnancy

**Hyperthyroidism:** overproduction of thyroid hormone by an overactive thyroid

**Hypothyroidism:** underproduction of thyroid hormone by an underactive thyroid

**Ishihara color charts:** tests for color-blindness

**Jod-Basedow effect:** iodine-induced hyperthyroidism, which occurs particularly as a result of excess iodine ingestion/administration in patients with multinodular goiter

**MALT:** mucosa-associated lymphoid tissue, the origin of many marginal-zone, B-cell thyroid lymphomas

**Multinodular goiter:** a thyroid with more than one nodule

**Myxedema:** a generalized non-pitting swelling of the skin that occurs in profound hypothyroidism – not to be confused with pretibial myxedema; also a synonym for profound hypothyroidism

**Papillary thyroid carcinoma:** a well-differentiated, thyroid carcinoma derived from follicular cells

**Pendred's syndrome:** autosomal-recessive condition characterized by deafness associated with goiter and mild hypothyroidism

**Pretibial myxedema:** a rare non-pitting, disfiguring skin infiltration that generally involves the anterior tibial region and dorsum of the foot; seen in association with Graves' disease

**Radio-iodine:** radioactive isotopes of iodine (either  $^{123}\text{I}$  or  $^{131}\text{I}$ ) taken up by thyroid tissue; can be used for thyroid imaging ( $^{123}\text{I}$  or  $^{131}\text{I}$ ), for imaging thyroid cancer ( $^{131}\text{I}$ ) or for therapy ( $^{131}\text{I}$ )

**Struma ovarii:** ectopic thyroid tissue comprising the bulk of an ovarian teratoma; may cause hyperthyroidism

**T3:** triiodothyronine or liothyronine; active thyroid hormone produced mainly by deiodination of T4 in the peripheral tissues, with a small amount produced and released by the thyroid

**T4:** tetraiodothyronine or levothyroxine (or L-thyroxine); the major (precursor) hormone product of the thyroid

**TBG:** thyroid-binding globulin; the major thyroid-hormone-binding protein in the blood; also called thyroxine-binding globulin

**THBR:** thyroid-hormone-binding ratio; an inverse measure of the serum binding proteins for thyroid hormone from which the amount of free T4 can be estimated

**Thionamides:** a group of drugs including propylthiouracil, methimazole (prescribed in the USA) and carbimazole (prescribed in the UK), used to inhibit synthesis of thyroid hormones in hyperthyroidism

**Thyroglobulin:** a high molecular weight protein on which thyroid hormones are synthesized; the storage form of thyroid hormone (a key component of colloid in the center of the thyroid follicles); serum thyroglobulin is a tumor marker for well-differentiated thyroid carcinoma

**Thyrotoxicosis:** any condition attributable to excess circulating thyroid hormone levels

**Toxic nodular goiter:** a multinodular goiter producing excess amounts of thyroid hormone

**TRH:** thyrotropin-releasing hormone; produced by the hypothalamus; stimulates the pituitary to produce TSH

**TSH:** thyroid-stimulating hormone; produced by the pituitary; stimulates the secretion of T4 and T3 by the thyroid

## Introduction

In recent years, thyroid function tests have become routinely available to almost all physicians. Clinical chemistry laboratories in the UK typically perform over 20 000 tests each year. This volume of testing is not unreasonable, given that abnormalities of thyroid function rival diabetes mellitus in terms of prevalence, and can affect any system of the body. In the UK and USA, palpable thyroid nodules are present in one in 20 of the population. As a result, all doctors can expect to encounter thyroid disease in one form or another.

Thyroid disorders can usually be managed satisfactorily, but there are traps for the unwary. The presentation of thyroid dysfunction is often atypical, particularly in the elderly. In addition, 'routine' thyroid function testing shows that subclinical thyroid disease is ten times more common than clinical disease – one in ten women in the UK and USA has subclinical disease – and this poses difficult questions of how and when to intervene. Similarly, ultrasonography shows that, worldwide, up to half of the population over 65 years of age has thyroid nodules.

Initiating treatment for thyrotoxicosis is relatively straightforward, but completing treatment to the patient's satisfaction can be more complex and can take several years. The management of thyroid disease during pregnancy and of thyroid eye disease poses particular challenges, while the effective treatment of hypothyroidism with thyroxine has recently been questioned by both researchers and patient groups.

In *Fast Facts: Thyroid Disorders* we aim to provide all the necessary information in a concise and practical format to enable the general physician to negotiate potential traps with confidence. Knowing when to test, when to treat and when to refer will result in the rapid initiation of appropriate therapy and, just as importantly, reduce the unnecessary anxiety that both physicians and patients feel when coping with these common conditions.

## Thyroid hormone synthesis and regulation

**Synthesis and secretion.** The thyroid is the main site of iodine uptake in the body, concentrating iodide from the blood against an electrochemical gradient through the action of the sodium iodide symporter, an internal membrane protein that resides in the thyroid epithelial cells. The enzyme thyroid peroxidase incorporates iodine into two hormones (Figure 1.1):

- liothyronine (containing three iodine atoms and also known as triiodothyronine or T3)
- levothyroxine (L-thyroxine; containing four iodine atoms and also known as tetraiodothyronine or T4).

T3 and T4 are stored in the form of thyroglobulin in the colloid of the thyroid follicles and are released when thyroid-stimulating hormone (TSH) from the pituitary gland stimulates the thyroid. T3 is the active form of the hormone; it has a shorter half-life (1 day) in the circulation than T4 (about 7 days). T3 binds to three thyroid hormone receptors, one that is largely restricted to the pituitary and two that are widely distributed.

The adult thyroid typically produces about 90 µg of T4 and 6 µg of T3 daily. More than 99% of circulating T4 and T3 is bound to protein: 70% of T4 is bound to thyroid-binding globulin (TBG; also known as thyroxine-binding globulin), 10–15% to thyroid/thyroxine-binding prealbumin (transthyretin) and 15–20% to albumin. When the concentration of binding proteins such as TBG increases or decreases, the serum concentration of T4 and T3 (which bind to these proteins) also increases or decreases, respectively. However, the free hormone concentrations remain normal.

**Peripheral conversion of T4 to T3.** About 80% of circulating T3 is produced enzymatically by the deiodination of T4 in peripheral tissues – mainly the liver and kidneys. T4 is converted to T3 in most tissues by two related enzymes, deiodinase types 1 and 2, while another enzyme,

deiodinase type 3, converts T4 to an inactive form of T3 (called reverse T3 or rT3). Thus, replacement of thyroid hormone with T4 alone provides a long-lasting store of thyroid hormone that is gradually converted to T3, resulting in stable plasma levels of both T4 and T3.

Direct thyroid production of T3 may increase in patients with iodine deficiency and in those whose thyroid is overstimulated by TSH or by anti-TSH-receptor antibodies, as occurs in patients with Graves' disease. Starvation, severe illness and many drugs impair the peripheral conversion of T4 to T3, which may cause a decrease in the metabolic rate. It is uncertain whether the resulting decrease in overall metabolic rate is beneficial or harmful.

**Feedback control.** T4 and T3 production is controlled by TSH from the pituitary gland, which itself is controlled by thyrotropin-releasing hormone (TRH) secreted by the hypothalamus (see Figure 1.1). Increases in the levels of circulating thyroid hormone (T3 and T4) suppress both TRH and TSH, completing the negative feedback loop. The pituitary appears to be less sensitive to circulating T3 than to T4, suggesting that intrapituitary conversion of T4 to T3 may be a better way of delivering T3 to the pituitary than circulating T3 itself.

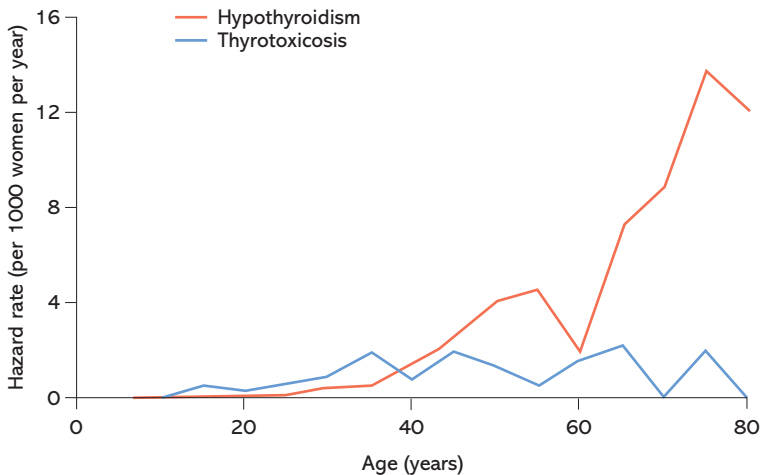
Serum TSH is exquisitely sensitive to small changes in serum thyroid hormone concentrations. For example, a 50% reduction in free T4 in the serum produces a ninetyfold increase in serum TSH concentration. The normal range of serum thyroid hormone concentrations is relatively broad; modest decreases or increases within this normal range indicate the earliest stage of thyroid disease and are reflected in serum TSH concentrations that move out of the normal range.

**Iodine intake.** The recommended daily intake of iodine for adults is 150–300 µg. Iodine levels can be measured in the urine, as this is the major route of iodine excretion. Iodine supplementation in the form of iodized salt is standard practice in many areas of the world, and many multivitamins also contain iodine, generally 150 µg/tablet.

Goiter, hypothyroidism and endemic cretinism are all significant risks when iodine intake falls below 50 µg/day. The highest iodine content is found in fish, with smaller amounts in milk, eggs and meat.

### Epidemiology

Clinical hyperthyroidism, defined as low thyroid-stimulating hormone (TSH) and raised T<sub>4</sub>, occurs in 0.5% of both the US and UK populations, while subclinical hyperthyroidism (TSH < 0.1 mU/L, T<sub>4</sub> in the normal range) occurs in a further 0.7%. An additional 2.5% of women and 0.6% of men may have a previous history of hyperthyroidism. TSH values just below the normal range often revert to normal on repeat testing. Thyrotoxicosis can occur at any age in the adult population (Figure 2.1). Although the risk of developing hyperthyroidism increases two- to fourfold with age, this is a less dramatic increase than that of hypothyroidism with age (five- to tenfold) – 10–20% of women over the age of 65 have subclinical hypothyroidism. Prevalence estimates for hyperthyroidism in the elderly population are about 4% for women and 1.5% for men.



**Figure 2.1** Risk for women of developing overt thyrotoxicosis (and hypothyroidism) at different ages. Redrawn with permission from Vanderpump MP et al.

Of patients with clinical thyrotoxicosis referred to endocrine clinics:

- 65% have Graves' disease
- 20% have toxic multinodular goiter
- 5% have a solitary toxic nodule
- the remaining 10% have transient thyroiditis or an unclear etiology.

In areas of low iodine intake, the proportion of patients with toxic multinodular goiter is higher. Graves' disease can occur at any age, although it is rare in childhood; it is 7–10 times more common in women. Toxic nodular disease is uncommon in patients under 40 years old and probably accounts for much of the increasing prevalence of hyperthyroidism with age. It is likely that many cases of hyperthyroidism that occur because of the spontaneous resolution of thyroiditis go undiagnosed.

## Etiology

The main causes of hyperthyroidism are summarized in Table 2.1, and are discussed in greater depth below. Measurement of radio-iodine uptake and a scan of radio-iodine distribution are very useful in the differential diagnosis of hyperthyroidism (see Chapter 3).

**Graves' disease**, also known as von Basedow's disease or diffuse toxic goiter, is an autoimmune condition in which anti-TSH-receptor antibodies stimulate the thyroid, hence the alternative name of thyroid-stimulating antibodies. Modern, sensitive assays are positive for these antibodies in more than 90% of cases, particularly in more severe cases of hyperthyroidism. Up to 70% of patients with Graves' disease have clinical or subclinical ophthalmopathy (see pages 32–34), which may occur because of low levels of TSH receptor expressed in the retro-orbital fibroblasts. Although the mechanism remains unclear, it appears that stressful life events are common in the 1–2 years preceding the onset of Graves' disease. Marked increases in the incidence of the disease have been reported in communities at war, for example a fivefold increase occurred during the civil war in the former Yugoslavia.

**Toxic nodular disease.** Most low TSH values in elderly patients are believed to be caused by nodular disease (see Chapter 7).