Thyrotoxicosis

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Abstract

Thyrotoxicosis refers to symptoms and signs that arise from excess quantities of circulating thyroid hormones. It can be caused by hyperthyroidism – hyperfunction of the thyroid gland – or by other mechanisms, such as the destruction of thyroid follicles with release of thyroid hormones (thyroiditis) or excessive ingestion of thyroid hormones (thyrotoxicosis factitia). There are several causes of thyrotoxicosis, the most common being Graves' disease, followed by toxic nodular thyroid disease (toxic multinodular goitre or toxic adenoma) and thyroiditis of any aetiology. Establishing the underlying cause of thyrotoxicosis is essential for its management. Diagnosis relies on clinical observation, sensitive hormonal and immunological assays and the occasional use of thyroid scintigraphy. Management of thyrotoxicosis includes the use of anti-thyroid medication, β-adrenoceptor blocking agents, radioiodine, thyroid surgery or a combination of these. Management of thyrotoxicosis in pregnancy and the postpartum period requires special attention and expertise as the correct diagnosis and treatment can significantly influence the outcome of pregnancy and the well-being of the mother and the fetus or newborn.

Keywords ^{131}I-Radioiodine; anti-thyroid medication; Graves' disease (GD); hyperthyroidism; MRCP; thyroid storm; thyroiditis; thyrotoxicosis; toxic adenoma; toxic multinodular goitre (TMNG)

Key points

- Thyrotoxicosis is one of the most common endocrine disorders, affecting 1–1.5% of the population
- Graves' disease is the most common cause, being responsible for approximately 80% of cases, followed by toxic nodular disease [toxic multinodular goitre (TMNG) or toxic adenoma (TA)] and thyroiditis of any cause
- Diagnosis of thyrotoxicosis is established by suppressed thyroid-stimulating hormone and elevated free thyroxine and/or free triiodothyronine concentrations
- Establishing the cause of thyrotoxicosis is required for its appropriate management
- Management of thyrotoxicosis includes the use of anti-thyroid drugs, β-adrenoceptor blocking agents, radioiodine administration and thyroid surgery, or a combination of these
- The most recent guidelines recommend more active treatment of subclinical thyrotoxicosis, especially in individuals >65 years of age

Introduction

Thyrotoxicosis denotes the clinical syndrome that results from tissue exposure to excess circulating free thyroid hormones – thyroxine (3,5,3′,5′-tetraiodo-L-thyronine; T4) and/or triiodothyronine (3,5,3′-triiodo-L-thyronine; T3). It represents one of the most common endocrine clinical presentations, affecting approximately 1–1.5% of population,[1] and occurs 5–10 times more often in women than men. Thyrotoxicosis results from several conditions (Table 1), although the vast majority of cases (up to 80%) are caused by Graves' disease (GD). Other common causes include toxic multinodular goitre (TMNG), toxic adenoma (TA) and thyroiditis of any aetiology.

Thyroid hormones influence metabolic rate and protein synthesis and have receptors that are present in virtually all human tissues. It is therefore not surprising that clinical signs and symptoms of thyrotoxicosis are pleiotropic (Table 2). Untreated or inadequately treated thyrotoxicosis results in an increased risk of atrial fibrillation, cardiovascular mortality, thromboembolic events, osteoporosis and neuropsychiatric states, as well as a significant impairment of quality of life.

Anatomy and physiology of thyroid hormone production

The thyroid is located in the anterior part of the lower neck, enclosed in the pre-tracheal fascia below the strap muscles of the neck. It consists of the isthmus, which lies horizontally just below the cricoid cartilage, two lateral lobes that extend upwards over the lower part of the thyroid cartilage and occasionally a pyramidal lobe. A normally sized thyroid weighs 15–20 g and is made up of follicles; these consist of a single layer of follicular cells (thyrocytes) that are surrounded by a rich capillary network. The interior of the follicles is filled with clear proteinaceous colloid that contains thyroglobulin.

Biosynthesis of thyroid hormones requires iodine as a substrate. Iodine uptake from the circulation is facilitated by active transport via the sodium/iodide symporter (NIS) in the basolateral membrane of the follicular cells. Iodine is transferred through the cell and across the apical membrane into the colloid. The next step is oxidation of iodine, which requires the enzyme thyroid peroxidase (TPO), localized at the apical membrane, and hydrogen peroxide. Oxidized iodine is quickly 'organified' onto the tyrosyl residues of thyroglobulin to form mono- or diiodothyronine (MIT or DIT). TPO then catalyses the coupling reaction in which two DIT molecules form a molecule of T4, and MIT and DIT form a molecule of T3. Finally, colloid containing thyroglobulin with T4 and T3 is endocytosed back into the thyrocyte;

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Causes of thyrotoxicosis

Hyperthyroidism

Excessive thyroid-stimulating hormone (TSH) — receptor stimulation

- Graves' disease[a] also known as von Basedow disease
- Gestational hyperthyroidism (hyperemesis gravidarum)
- Trophoblastic disease[c]
- TSH-producing pituitary adenoma[d]
- Resistance to thyroid hormone (RTH)[d]
- Familial non-autoimmune autosomal dominant hyperthyroidism (FNAH) persistent sporadic congenital non-autoimmune hyperthyroidism (PSNAH)[d]

Autonomous thyroid hormone secretion

- Toxic multinodular goitre (TMNG)[b]
- Toxic adenoma (TA)[b]

Excess iodine

- Investigations with iodinated contrast
- Amiodarone[e]

Thyrotoxicosis without hyperthyroidism

Destruction of thyroid follicles with release of hormones — thyroiditis

- Autoimmune thyroiditis (silent thyroiditis, painless thyroiditis, lymphocytic thyroiditis, Hashimoto's thyroiditis)/postpartum thyroiditis
- Subacute thyroiditis (de Quervain's thyroiditis, post-viral or granulomatous thyroiditis)[c]
- Acute thyroiditis (bacterial or fungal)[d]
- Drug-induced thyroiditis (amiodarone,[e] lithium, interferon-α, interleukin-2, granulocyte—macrophage colony-stimulating factor (GM-CSF), multi-targeted receptor tyrosine kinase inhibitors (sunitinib, sorafenib, etc.))

Extrathyroidal sources of thyroid hormone

- Thyrotoxicosis factitia — ingestion of excess thyroid hormones (iatrogenic, involuntary, surreptitious)
- Metastatic thyroid carcinoma (mostly differentiated follicular carcinoma)[d]
- Struma ovarii (functional thyroid tissue in an ovarian teratoma)[d]

[a] Very common.
[b] Common.
[c] Rare.
[d] Extremely rare.
[e] Amiodarone has pleiotropic effects on the thyroid (see main text).

Table 1

Clinical features of thyrotoxicosis (independent of aetiology)

Cardiovascular system

- Palpitations[a], sinus tachycardia[a], atrial fibrillation[a], congestive (high-output) heart failure

Autonomic nervous system

- Fine tremor[a], heat intolerance[a], excess sweating[a]

Central nervous system

- Hyperactivity[a], irritability[a], sleep disturbance[a], dysphoria, psychosis, depression ('apathetic thyrotoxicosis' in elderly individuals), fatigue[a], hyperreflexia, hyperkinesia, chorea, hyperkalaemic periodic paralysis (primarily in young Asian men)

Gastrointestinal system

- Increased appetite[a], weight loss[a] (weight gain in around 10% of patients), increased stool frequency

Respiratory system

- Dyspnoea

Genitourinary system

- Polyuria, polydipsia
- Oligomenorrhoea or amenorrhoea, erectile dysfunction, loss of libido

Musculoskeletal system

- Muscle weakness, proximal myopathy, osteoporosis

Eyes

- Retraction of the upper or lower eyelid (a visible rim of sclera between the lid and the limbus, responsible for the typical 'stare' of the patient), lid lag (upper lid lags behind the globe when the patient is asked to shift the gaze downwards)

Skin and hair

- Warm and moist skin[a], pruritus, hair loss[a], onycholysis[a], palmar erythema

[a] Signs and symptoms that occur commonly.

Table 2

the T4 and T3 are released from thyroglobulin in the lysosomes and are subsequently secreted into the circulation.

Most (>99%) of the T4 and T3 in the circulation is reversibly bound to thyroxine-binding globulin (TBG), transthyretin (TTR) or albumin. It is, however, the free fraction of thyroid hormones that correlates with the metabolic state. The active form of thyroid hormone is free T3 (fT3). This binds to the nuclear thyroid hormone receptors, and this complex initiates transcriptional changes resulting in its physiological effects. Three iodothyronine deiodinases (D1—D3) regulate the availability of fT3 for the tissues. D1 (mainly in liver and kidney) catalyses 5′-deiodination of T4 to form T3 and is responsible for producing most of the T3 in the circulation. D2 contributes towards the T3 pool in the circulation and plays a role in T3 generation in the hypothalamus and pituitary. D3 is the main inactivating enzyme catalysing 5-deiodination of T4 to form the inactive reverse T3 (rT3).

Free T4 (fT4) and fT3 regulate the secretion of hypothalamic thyrotrophin-releasing hormone (TRH) and hypophyseal thyroid-stimulating hormone (TSH) via a classic negative feedback loop. TSH acts through TSH receptors (TSHR) on the basolateral membrane of the thyrocytes, resulting in stimulation of thyroid hormone production and trophic effects on the thyroid.

Laboratory diagnosis

Hyperthyroidism is characterized by suppressed or undetectable concentrations of TSH and elevated fT4 and/or fT3 concentrations. 'T3-toxicosis' refers to an isolated elevation of fT3 in the context of a suppressed serum TSH concentration. Subclinical hyperthyroidism refers to a suppressed TSH concentration with normal concentrations of fT4 and fT3.

Rarely, serum TSH concentrations are elevated (or inappropriately normal) in the context of elevated fT4 and/or fT3 concentrations; this is defined as secondary hyperthyroidism caused by resistance to thyroid hormone (RTH) or a TSH-secreting

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