Austin Journal of Endocrinology and Diabetes

Open Access

Austin Publishing Group

Review Article

Hyperthyroidism: Definition, Causes, Pathophysiology and Management

Bereda G*
Department of Pharmacy, Negelle Health Science College, Guji, Ethiopia

***Corresponding author:** Gudisa Bereda, Department of Pharmacy, Negelle Health Science College, Guji, Ethiopia

Received: December 20, 2021; **Accepted:** January 20, 2022; **Published:** January 27, 2022

Abstract

Hyperthyroidism is defined as the excess production and release of thyroid hormone by the thyroid gland resulting in inappropriately high serum levels. Hyperthyroidism can affect multiple organ systems, including the cardiovascular, nervous, gastrointestinal, and hepatic systems. The most common form of hyperthyroidism is caused by increased thyroid hormone production in Graves' disease, and the others are toxic multinodular goiter and solitary toxic adenoma. Graves' disease is the most common cause of hyperthyroidism in developed countries. It is an autoimmune condition in which antibodies against the thyroid-stimulating hormone receptor cause unopposed stimulation of the thyroid gland. The hypothalamus releases thyroid-releasing hormone, which stimulates the pituitary to release thyroid-stimulating hormone, in turn stimulating the thyroid gland to release thyroid hormones, T4 and T3. The increased production of thyroid hormone normally causes inhibition of thyroid-releasing hormone and thyroid-stimulating hormone release by the hypothalamus and pituitary respectively. Surgical removal of the thyroid gland in patients if with large gland (>80g), severe ophthalmopathy, and lack of remission is present. Thyroid surgery is rapid and effective but invasive and expensive. Propylthiouracil and methimazole block thyroid hormone synthesis by inhibiting the peroxidase enzyme system of the thyroid gland, thus preventing oxidation of trapped iodide and subsequent incorporation into iodotyrosines and ultimately iodothyronine ("organification"); and by inhibiting coupling of methimazole and diiodotyrosine to form thyroxine and triiodothyronine and also propylthiouracil (but not methimazole) also inhibits the peripheral conversion of thyroxine to triiodothyronine. Glucocorticoids are used in thyrotoxicosis in which iodine produces a destroying effect on the thyroid tissue, such as in the initial phases of subacute thyroiditis or in type-2 amiodarone induced thyrotoxicosis.

Keywords: Causes; Definition; Hyperthyroidism; Management; Pathophysiology

Abbreviations

AIH: Amiodarone-Induced Hyperthyroidism; DIT: Diiodotyrosine; FT3: Free-Triiodothyronine; MIT: Monoiodotyrosine; MMI: Methimazole; PTU: Propylthiouracil; RAI: Radioactive Iodine Therapy; RAIU: Radioactive Iodine Uptake; STA: Solitary Toxic Adenoma; T4: Thyroxine; T3: Triiodothyronine; TMG: Toxic Multinodular Goiter; TRH: Thyroid-Releasing Hormone; TSH: Thyroid-Stimulating Hormone

Introduction

Thyroid hormones act on almost all nucleated cells and are essential for normal growth and energy metabolism [1]. Iodine is an essential requirement for thyroid hormone synthesis and in the adult the recommended daily iodine intake is 150mg. Excess iodine ingestion (up to 150mg/d) also decreases the release of thyroxine (T4) and triiodothyronine (T3) from the thyroid resulting in small decreases in serum T4 and T3 concentrations with compensatory increases in basal and TRH stimulated thyrotropin (TSH) concentrations, all values remaining well within the normal range [1]. The complex inverse association between the pituitary derived thyroid stimulating hormone (TSH) and the thyroid hormones, free thyroxine (FT4) and free tri-iodothyronine (FT3), renders TSH the more sensitive marker of thyroid status [2]. Hyperthyroidism is defined as the excess production and release of thyroid hormone by the thyroid gland resulting in inappropriately high serum levels. The disproportionate amount of thyroid hormone leads to an accelerated metabolic state [3]. Hyperthyroidism is a common condition with a wide variation in the reported incidence, reflecting various factors such as differences in dietary iodine intake, ethnical origin, and population structure. Hyperthyroidism is the most common cause of thyroid dysfunction in areas with mild and moderate iodine deficiency [4]. Occurrences are seen at all ages but presentation peaks between 20 and 50 years of age secondary to the higher prevalence of Graves' disease. Toxic multinodular goiter typically occurs after age 50 years, as opposed to toxic adenoma, which presents at a younger age. All forms of thyroid disease are more common in women [3]. Subclinical hyperthyroidism is defined by a serum TSH level that is below the statistically defined lower limit along with a serum free thyroxine (fT4) level within the normal reference range. Its prevalence is higher in iodine-insufficient areas, and although it increases with age, it still is relatively common in women of childbearing age [5]. Hyperthyroidism can affect multiple organ systems, including the cardiovascular, nervous, gastrointestinal, and hepatic systems. The

Citation: Bereda G. Hyperthyroidism: Definition, Causes, Pathophysiology and Management. Austin J Endocrinol Diabetes. 2022; 9(1): 1091.

interaction between the thyroid and liver is critical for maintaining homeostasis in both sites. Thyroid hormones are glucuronidated and sulfated within the liver and subsequently excreted into bile; in addition, these hormones maintain the metabolism of bilirubin by playing a role in the enzymatic activity of glucuronyltransferase and by regulating the level of ligandin, a major organic anion-binding protein [6]. A very small portion of the daily production of thyroxin (T4) and triiodothyronine (T3), less than 10%, is excreted in the stool. In people with normal thyroid function, this pathway of T4 and T3 recirculation contributes so little to hormone availability that patients who have gastrointestinal disease or are receiving drugs that decrease T4 absorption do not have abnormal thyroid function. However, the thyrotoxic states are characterized by an increased enterohepatic circulation of thyroid hormones, as well as by an increased urinary and fecal excretion of both conjugated and free T4. Thyroiditis, inflammation of the thyroid gland resulting in release of stored hormone, is a frequent cause of thyrotoxicosis. The clinical presentation of thyrotoxicosis varies from asymptomatic (subclinical) to life threatening (thyroid storm). Thyroid storm is a true endocrine emergency. In thyroid storm there is hyper metabolism, and excessive adrenergic activity, death may occur due to heart failure and shock. Hyperthyroidism is more common among women and affects around 2% of women and 0.2% of men. The most common form of hyperthyroidism is caused by increased thyroid hormone production in Graves' disease (GD), and the others are toxic multinodular goiter (TMNG) and solitary toxic adenoma (STA) [6,7].

Nodular thyroid disorders are more prevalent in iodine deficiency while autoimmune thyroid disorders including Hashimoto's thyroiditis and Graves' disease occur more frequently in iodine-replete populations. However, a multitude of other risk factors including genetic and ethnic susceptibility, gender, smoking, alcohol consumption, presence of other auto-immune conditions, syndromic conditions and drug exposures also influence thyroid disease epidemiology [1].

Graves' disease

Graves' disease is the most common cause of hyperthyroidism in developed countries. It is an autoimmune condition in which antibodies against the TSH receptor cause unopposed stimulation of the thyroid gland. Graves' disease affects about 0.5% of the population, predominantly patients in the age group 40 to 60 years with a female to male ratio of 5:1 to 10:1. Circulating thyroid antibodies activate the thyroid stimulating hormone (TSH) receptor and stimulate thyroid follicular hypertrophy and hyperplasia with increases in thyroid hormone production. Graves' disease is characterized by hyperthyroidism and diffuse goiter; ophthalmopathy, pretibial myxedema and thyroid achropachy may also be observed. The pathogenesis of this enigmatic condition remains incompletely understood but the central pathogenetic event is the unregulated stimulation of the TSH receptor by autoreactive TSH receptor antibodies (TRAbs). Graves' disease has been described throughout the globe and predominantly affects women (female: male ratio 8:1), typically in their 3rd to 5th decades of life [1,8]. Individuals with a family history of hyperthyroidism or other autoimmune diseases such as pernicious anemia, myasthenia gravis, type I diabetes mellitus, and celiac disease has an increased propensity of developing Graves.

Pathogenesis Graves' disease

The cause of Graves' disease remains unclear, but it is believed to result from a complex interaction between genetic background (heredity), environmental factors and the immune system. For unknown reasons, the immune system produces an antibody (TSH receptor antibody (TRAb)) that stimulates the thyroid gland to produce excess thyroid hormone. Genetic susceptibility to the disease is thought to be polygenic. Graves' disease has been reported to be associated with the human leukocyte antigen (HLA) gene on chromosome 6p, the cytotoxic T lymphocyte antigen-4 (CTLA-4) gene on chromosome 2q33, and the lymphoid tyrosine phosphatase (PTPN22) gene on chromosome 1p13. In Graves' disease, hyperthyroidism results from the action of thyroid-stimulating antibodies (TSAb) directed against the thyrotropin receptor on the surface of the thyroid cell. The thyroid-stimulating immunoglobulin (TSI) binds to and stimulates the TSH receptor on the thyroid cell membrane resulting in follicular cell growth, vascularity increase, and in excessive synthesis and secretion of thyroid hormone. The thyroid gland typically displays lymphocytic infiltration, with T-lymphocyte abnormality and absence of follicular destruction. T cells activate local inflammation and tissue remodelling by producing and releasing cytokines, leading to B-cell dysregulation and increase in autoantibody production. An imbalance between pathogenic and regulatory T cells is thought to be involved in both the development of Graves' disease and its severity [9].

Toxic multinodular goiter (TMNG)

Toxic multinodular goiter (TMNG) is an important cause of hyperthyroidism. It is caused by unwarranted release of thyroid hormones from multiple autonomously functioning nodules in the thyroid gland. It is more common in areas of dietary iodine deficiency (third-world countries) and in the elderly (poor diet). TMNG is more common than Graves' disease in the elderly [3].

Toxic nodular goitre (toxic adenoma)

Toxic nodular goitre is the most frequent cause of thyrotoxicosis in the elderly, especially in iodine deficient areas. Solitary toxic nodules are more common in women than in men with a 1:5 M:F ratio reported in some studies. An autonomous thyroid nodule (toxic adenoma) is a discrete thyroid mass whose function is independent of pituitary control [1,10].

Subacute thyroiditis

Thyroiditis is characterized by a self-limiting course of thyrotoxicosis, followed by hypothyroidism, and then return to normal thyroid function or is inflammation of the thyroid gland that typically follows a viral upper respiratory infection and causes additional release of preformed thyroid hormone. It is slightly more common in females than males (ratio of 1.5:1) and permanent hypothyroidism occurs in 10-20% of cases. Acute painful thyroiditis often presents following a respiratory tract infection, while painless thyroiditis may occur post-partum in up to 9% of otherwise normal women [1,11].

Suppurative thyroiditis

Suppurative thyroiditis is an infection of the thyroid gland typically caused by bacteria but can be caused by fungus, mycobacteria, or parasites. It is most common in immunocompromised individuals

or those with underlying thyroid disease. It presents with a tender erythematous anterior neck mass, fever, dysphagia, and dysphonia [3].

Drug induced hyperthyroidism

Amiodarone-induced hyperthyroidism (AIH): Amiodarone, a benzofuranic derivative containing 75 mg of iodine per 200-mg tablet, is widely used for the long-term treatment of cardiac arrhythmias. Amiodarone inhibits the 5'monodeiodination of T4 in the liver and pituitary, thereby decreasing serum T3 and mildly increasing serum T4 levels without altering TSH concentrations. Type 1 AIT is due to the high iodine content of amiodarone. It occurs in areas of iodine deficiency and in patients with underlying thyroid disorders, such as multinodular goiter. In Type 1 AIT, the thyroid gland produces and releases excessive amounts of thyroid hormone. In contrast, Type 2 AIT results from a destructive process in the thyroid gland in which preformed thyroid hormones leak from the damaged follicular cells in patients without underlying thyroid disease. Amiodarone induced thyrotoxicosis is more common in iodine deficient areas and appears to be more common in men [1,12]. Amiodarone-induced hyperthyroidism (AIH) is much more common and challenging to treat than amiodarone-induced hypothyroidism. Amiodarone-induced thyrotoxicosis results from two different mechanisms. The iodine released during the metabolism of the drug is responsible for the thyrotoxicosis in most cases. Predisposing factors include micronodular and macronodular goiter, which are common in older patients who most often require amiodarone. Thyroid autoimmunity has also been incriminated as a predisposing factor and antithyroid antibodies have been found following amiodarone administration in some patients but not in others [3].

Other drugs that cause thyrotoxicosis include interferon-α, lithium, tyrosine kinase inhibitors, highly active antiretroviral therapies, immune checkpoint mediators and the humanized monoclonal antibodies used in the treatment of multiple sclerosis. Although these drugs may cause transient thyrotoxicosis through destructive thyroiditis the immune modifying agents such as interferon-α, HAART, and alemtuzumab may in addition induce Graves' diseases through less well-defined immune reactivation mechanisms [1].

Iodine induced hyperthyroidism

Iodine-induced hyperthyroidism, the Jod-Basedow phenomenon, is commoner in older persons with long standing nodular goitre and in regions of chronic iodine deficiency undergoing iodine supplementation. Iodisation programs temporarily increase the risk of iodine induced hyperthyroidism; the risks are principally to the elderly who may have coexisting cardiac disease and also to those with limited access to healthcare [1,13]. Iodide-induced hyperthyroidism may occur in patients with iodine-deficiency goiter, in euthyroid Graves' disease patients after antithyroid drug therapy, in euthyroid subjects with previous spontaneous and iatrogenic episodes of thyroid dysfunction, in patients with multinodular goiters who reside in areas of iodine repletion or deficiency and in people with no evidence of underlying thyroid disease [2].

Postpartum thyroiditis

Postpartum thyroiditis is inflammation of the thyroid gland following delivery. It is a transient form of hyperthyroidism that can develop 6 weeks to 6 months postpartum with a significant chance of recurrence in subsequent pregnancies. Patients present with painless goiter and typically have significant family history of autoimmune disease [3].

Pathophysiology

The production and release of thyroid hormones is regulated by a sensitive negative feedback loop involving the hypothalamus, pituitary gland, and thyroid gland. The hypothalamus releases thyroid-releasing hormone (TRH), which stimulates the pituitary to release TSH, in turn stimulating the thyroid gland to release thyroid hormones, T4 and T3. The increased production of thyroid hormone normally causes inhibition of TRH and TSH release by the hypothalamus and pituitary respectively. Disruption of this delicate system leads to additional production and release of thyroid hormone and subsequent hyperthyroidism. TSH-secreting pituitary tumors release biologically active hormone that is unresponsive to normal feedback control. The tumors may co-secrete prolactin or growth hormone; therefore, patients may present with amenorrhea, galactorrhea, or signs of acromegaly. Hyperthyroidism usually occurs with larger nodules (>3 cm in diameter). Thyrotoxicosis occurs when the autonomous follicles generate more thyroid hormone than is required. The production of thyroid hormones in the thyroid gland depends on iodine. Dietary iodide is transported into cells and converted to iodine. The iodine is then bound to thyroglobulin by thyroid peroxidase and subsequently forms monoiodotyrosine (MIT) and diiodotyrosine (DIT). The MIT and DIT are coupled to form T4 and T3 respectively. T3 is more biologically active and is typically formed in the periphery by conversion of T4 to T3. In the serum, thyroid hormone is typically bound to protein and inactive. Any process that increases the amount of unbound (free) thyroid hormone has the potential to cause thyrotoxicosis [3,7].

Clinical manifestations

Symptoms of thyrotoxicosis include nervousness, anxiety, palpitations, emotional lability, easy fatigability, heat intolerance, loss of weight concurrent with an increased appetite. Physical signs of thyrotoxicosis may include warm, smooth, moist skin and unusually fine hair, separation of the ends of the fingernails from the nail beds (onycholysis), retraction of the eyelids and lagging of the upper lid behind the globe upon downward gaze (lid lag), tachycardia at rest, widened pulse pressure, and a systolic ejection murmur; occasional gynecomastia in men [1].

Diagnosis

An elevated 24-hour radioactive iodine uptake (RAIU) indicates true hyperthyroidism: the patient's thyroid gland is overproducing T4, T3, or both (normal RAIU 10% to 30%). TSH-induced hyperthyroidism is diagnosed by evidence of peripheral hyper-metabolism, diffuse thyroid gland enlargement, elevated free thyroid hormone levels, and elevated serum immuno-reactive TSH concentrations. TSH-secreting pituitary adenomas are diagnosed by demonstrating lack of TSH response to thyrotropin-releasing hormone stimulation. In thyrotoxic Graves' disease, there is an increase in the overall hormone production rate with a disproportionate increase in T3relative to T4 [4].

Treatment

The aim of therapy is to monitor the condition of hyperthyroidism using medical, radioiodine or surgical treatment. Therapeutic objectives for hyperthyroidism are: to normalize the production of thyroid hormone; minimize symptoms and long-term consequences; provide individualized therapy based on type and severity of disease, patient age and gender, existence of non-thyroidal conditions, and response to previous therapy. Treatment strategies include antithyroid drugs, radioactive iodine, thyroid surgery, and medications for symptom control.

Non-pharmacologic therapy

Surgical removal of the thyroid gland in patients if with large gland (>80g), severe ophthalmopathy, and lack of remission is present. Thyroid surgery is rapid and effective but invasive and expensive. Patients need to be euthyroid before surgery. It can cause permanent hypothyroidism and transient hypocalcemia requiring calcium supplementation. Surgical complications include recurrent laryngeal nerve damage and permanent hypoparathyroidism. Because of the efficacy of antithyroid medication and radioactive iodine therapy, surgery is performed less frequently. It is generally reserved for pregnant women intolerant of thionamides, children with severe disease, severe ophthalmopathy, amiodarone-induced refractory disease, or unstable cardiac conditions. In the past, stress in the operating room during surgery was the most common cause of thyroid storm, with a mortality of 50%. Thyroid storm during surgery is exceedingly rare now with preoperative therapies including propranolol, antithyroid medication, and iodine. If thyroidectomy is planned, propylthiouracil (PTU) or methimazole (MMI) is usually given until the patient is biochemically euthyroid (usually 6 to 8 weeks), followed by the addition of iodides (500mg/day) for 10 to 14 days before surgery to decrease the vascularity of the gland. Evothyroxine may be added to maintain the euthyroid state while the thionamides are continued. Propranolol can be used for several weeks preoperatively and 7 to 10 days after surgery to maintain a pulse rate less than 90 beats/min [3].

Antithyroid pharmacotherapy

The mainstay of drug therapy is inhibition of thyroid hormone synthesis with thionamides. The duration of antithyroid medications is considered to be 12 to 18 months.

Thionamides

The most commonly used antithyroid drugs are the thionamides, propylthiouracil (PTU) and methimazole (MMI). PTU and MMI block thyroid hormone synthesis by inhibiting the peroxidase enzyme system of the thyroid gland, thus preventing oxidation of trapped iodide and subsequent incorporation into iodotyrosines and ultimately iodothyronine ("organification"); and by inhibiting coupling of MIT and DIT to form T4 and T3 and also PTU (but not MMI) also inhibits the peripheral conversion of T4 to T3. MMI and PTU are actively concentrated by the thyroid against a concentration gradient. Their primary effect is to inhibit the intra- and extra-thyroid hormonal synthesis. Intra-thyroid effects act through inhibition of iodide organification, inhibition of iodide incorporation in the thyrosine residues of thyroglobulin and inhibition of pairing of iodothyrosines. Extra-thyroid effects act through inhibition of the conversion of T4 to T3, due to the blocking of deiodinase-type-1 action. It has been reported that PTU, but not MMI, reacts with the selenenyl iodide intermediate of deiodinase-type-1 to form a selenenyl sulfide and thereupon blocking the conversion of T4 to T3 during the monodeiodination reaction and inhibition of thyroid-hormone transcriptional effects, due to the impaired bound to T3 nuclear receptors and to the recruitment of co-suppressor, and / or to the dissociation of co-activators [14-16]. Antithyroid drugs can be used both in the primary treatment of hyperthyroidism (long-term therapy: 1-2 yr) and as a preparation for radiometabolic or surgical treatment (short-term therapy: weeks or months). The elective indications for pharmacological therapy are: mild or moderate hyperthyroidism, slight increase of gland volume, pediatric or adolescent age, pregnancy or breast-feeding, and ophtalmopathy that could be worsened by radiometabolic therapy. The serum half-life of MMI is 6 to 8 hours whereas the half-life of PTU is 1 to 2 hours. In addition MMI has been found to have measurable intrathyroidal concentrations up to 20 hours [14]. The starting dose of CBZ/MMI is usually between 20 to 40 mg/day depending on the severity of the hyperthyroidism. PTU is started at between 100 to 150 mg 3 times a day with 100 mg of PTU considered equal to about 10 mg of CBZ/MMI. The initial high dose of the drugs can be tapered down after 4 to 8 weeks in what is referred to as the titration regimen. A maintenance dose of 5 to 20 mg of MMI or equivalent is achieved by about 4 to 6 months and this is continued for 12 to 18 months. The block–replace regimen refers to the option of maintaining the high dose of antithyroid drugs while adding levothyroxine to maintain euthyroidism [17].

The rationale use of MMI: First-choice antithyroid is preferable for the following reasons: a more rapid normalisation of serum thyroid hormone levels, less frequent occurrence of major, life-threatening side effects and wider availability (PTU is not available in many countrie) [17].

The side effects of MMI and PTU: Minor adverse reactions include pruritic maculopapular rashes, arthralgias, fever, and a benign transient leukopenia (<4,000/mm^3). Major adverse effects include agranulocytosis (with fever, malaise, gingivitis, oropharyngeal infection, and a granulocyte count <250/mm3), polymyositis, GI intolerance, hepatotoxicity, and hypoprothrombinaemia. If it occurs, agranulocytosis almost always develops in the first 3 months of therapy; routine monitoring is not recommended because of its sudden onset [18].

Radioactive iodine therapy

Radioactive iodine (131I) is the most commonly used form of treatment in the United States. It is safe, the principal side effect being the early or late development of hypothyroidism, necessitating life-long thyroid hormone replacement following 131I treatment. Radioactive iodine therapy can be used in Graves' disease, toxic nodules, and TMNGs. It is the most common form of therapy for adults with Graves' disease. Therapy is provided by a single oral dose of radioactive iodine that is absorbed by the thyroid gland and causes organ-specific inflammation. Continuous radiation to thyroid cells results in extensive local destruction and thyroid gland is ablated over a period of 6 to 18 weeks. Treatment with 131I does not cause a reduction in fertility and does not cause cancer, nor has it been shown to produce ill effects in offspring of those so treated prior to pregnancy.

It is contraindicated during pregnancy. The aim of RAI treatment is to destroy sufficient thyroid tissue to cure hyperthyroidism by rendering the patients either euthyroid or hypothyroid. Although it is highly effective, with a cure rate approaching 100% after one or more treatments, it has proved impossible to titrate doses for individual patients accurately to guarantee an euthyroid state [19]. RAI treatment is effective in children with hyperthyroidism due to GD, and most patients can be successfully treated with a single oral dose. Radioactive iodine should be seen at 4- to 6-week intervals for the first 3 months following radioactive iodine therapy, and then at intervals as the clinical situation dictates. Sodium iodide 131 is an oral liquid that concentrates in the thyroid and initially disrupts hormone synthesis by incorporating into thyroid hormones and thyroglobulin. Over a period of weeks, follicles that have taken up RAI and surrounding follicles develop evidence of cellular necrosis and fibrosis of the interstitial tissue. RAI is the agent of choice for Graves' disease, toxic autonomous nodules, and toxic multinodular goiters. Pregnancy is an absolute contraindication to the use of RAI [3,17].

Antithyroid Drugs of Second Choice

Potassium perchlorate

Perchlorate is the dissociated anion of perchlorate salts. It is rapidly absorbed from the gastrointestinal tract after oral administration. Perchlorate can be used in the treatment of thyrotoxicosis due to excess of exogenous iodine, particularly in type1 amiodarone-induced thyrotoxicosis. The drug competitively inhibits iodide uptake in the thyroid gland by competitively binding with NIS and also has the ability to discharge iodine from the thyroid gland, reducing intrathyroidal iodine, thereby decreasing thyroid hormone synthesis and accelerates its release. The initial dose is 250mg every 6 h by oral administration. It must be underlined that this substance can produce various side effects, among which the most serious is bone-marrow depression, which can lead to medullary aplasia. Perchlorate side effects are gastrointestinal irritation, rashes, drug fever, lymphadenopathy, nephrotic syndrome, and agranulocytosis [14,17,20].

Beta blockers

Many of the symptoms of hyperthyroidism such as sweating, anxiety, tremor and palpitations are caused by increased sympathetic activity and can be controlled rapidly by beta blockers. Propranolol in relatively high doses of over 160 mg per day can mildly inhibit conversion of T4 to T3. Administering beta blockers such as atenolol 50 to 100 mg or nadolol 40 to 80 mg once daily can be used to improve medication compliance. In the absence of contraindications such as asthma, beta blockers are used in the first few weeks of treating hyperthyroidism while awaiting the effect of antithyroid medications. They may also be used when antithyroid medications are withdrawn for treating with RAI. Rate-limiting calcium channel blockers may be used if there are contraindications for beta blockers [17]. β-Blockers are usually used as adjunctive therapy with antithyroid drugs, RAI, or iodides when treating Graves' disease or toxic nodules; in preparation for surgery; or in thyroid storm. It is primary therapy only for thyroiditis and iodine-induced hyperthyroidism.βBs are contraindicated in patient with decompensated heart failure sinus bradycardia, concomitant therapy with MAO inhibitors or tricyclic antidepressants, and patients with spontaneous, hypoglycemia.

Side effects of beta blockers: Includes hypersensitivity reactions (skin rashes, drug fever, rhinitis, conjunctivitis), salivary gland swelling; "iodism" (metallic taste, burning mouth and throat, sore teeth and gums, symptoms of a head cold, and sometimes stomach upset and diarrhea); gynecomastia [14].

Lithium Carbonate

There are two lithium carbonate preparations, namely, immediate-release and sustained release. The immediate-release and sustained-release preparations reach a peak plasma concentration at about 1-2 hours and 4-5 hours after administration, respectively. The elimination half-life of lithium is about 18–36 hours, and it is mostly excreted by the kidneys. Lithium clearance is considered to decrease with aging and renal impairment. Lithium is concentrated by the thyroid gland at a level 3 to 4 times of that in the plasma, probably by active transport. The primary mechanism of lithium is the inhibition of thyroid hormone release by inhibiting the action of TSH on cAMP. Lithium may also inhibit thyroid hormone synthesis. In hyperthyroidism patients, serum thyroxine mostly decreased to around 25–32% of baseline at 1 week after lithium treatment and decreased to around 35% of baseline at 2 weeks after treatment. Lithium is not the principal treatment of hyperthyroidism because of its side effects and a narrow therapeutic range. However, it can be used to temporarily control hyperthyroidism in patients who cannot use thionamide drugs. Lithium can also be prescribed as an alternative therapy in thyroid storm treatment. The dose of lithium is 300-450 mg taken orally every 8 hours. Elderly patients require a lower dose of lithium to maintain the therapeutic level because they have a decrease in total body water and glomerular filtration rate. Lithium is not the first-line treatment of type 1 amiodarone-induced thyrotoxicosis (AIT), but few studies have used lithium as adjuvant treatment.

Side effect of lithium carbonate: Symptoms of chronic intoxication can be classified to mild, moderate, and severe toxicity. The symptoms of mild toxicity (lithium level 1.5-2 mEq/L) include nausea, vomiting, diarrhea, hand tremor, and drowsiness while the symptoms of moderate toxicity (level 2-2.5 mEq/ L) include myoclonic twitches, nystagmus, dysarthria, ataxia, and confusion. Severe toxic symptoms (level > 2.5mEq/L) are renal impairment, impaired consciousness, seizure, coma, and death. Precipitating factors of chronic lithium toxicity might be an increase in the dose of the lithium regimen, a decline in renal function decline, or receival of some medications such as thiazides, nonsteroidal anti-inflammatory drugs, and angiotensin-converting enzyme inhibitors. These medications increase renal reabsorption of lithium, causing increased serum lithium concentration. However, toxic symptoms may occur even in the therapeutic range of lithium [17,20].

Glucocorticoids

The main mechanism of glucocorticoids in controlling thyrotoxicosis is their inhibitory effect on peripheral T4 to T3 conversion. Glucocorticoids are used in thyrotoxicosis in which iodine produces a destroying effect on the thyroid tissue, such as in the initial phases of subacute thyroiditis or in type-2 amiodarone induced thyrotoxicosis. Type 2 AIT is treated with oral

glucocorticoids while Type 1 AIT is treated with thionamides. The effect of the glucocorticoids is twofold, anti-inflammatory action and a reduction in the peripheral conversion of T4 into T3. One can use methylprednisolone at a dose of 20-40 mg/die or dexamethasone at a dose of 3-6 mg/die, achieving euthyroidism generally within 1-3 weeks. Steroids are gradually reduced and suspended only 2-3 months after the start of the treatment in order to avoid possible relapses [14,17].

Cholestyramine

Cholestyramine is an ionic exchange resin sequesters T4 in the intestine and increases its fecal excretion. Both T3 and T4 are concentrated in the liver and secreted in the bile in conjugated form and a small amount in unconjugated form. Free hormones are released by bacterial enzyme deconjugation in the large intestine and reabsorbed to the blood circulation, completing the enterohepatic circulation of thyroid hormone. Experimentally, it has been shown that 50mg of cholestyramine can bind approximately 3000 lg of T4 and therefore can enhance the clearance of thyroid hormones. Because of the increased enterohepatic circulation of thyroid hormones during hyperthyroidism, attempts have been made to sequester these hormones in the intestine using ionic exchange resins. Cholestyramine therapy has been studied in the treatment of thyrotoxicosis as an adjunctive therapy to thionamides, and has been found to decrease thyroid hormone levels rapidly [20,21].

The common side effects of Cholestyramine

The Common effects are bloating, flatulence, and constipation. Since cholestyramine might bind to other drugs given concomitantly, it is generally recommended that other drugs be taken at least 1 hour before or 4 to 6 hours after cholestyramine.

Iodine-Containing Compounds

These are rarely used for the rapid control of hyperthyroidism in the context of thyroid storm or in the preoperative preparation for thyroid surgery. Iodine was used to treat hyperthyroidism before the discovery of thionamide antithyroid drugs. The iodine-containing compounds used in the treatment of hyperthyroidism are potassium iodide (KI) in the form of KI tablets, a saturated solution of potassium iodide (SSKI), and Lugol's solution. SSKI is prepared by adding KI crystals to water until the saturation point of KI is reached. Lugol's solution is an aqueous solution of elemental iodine and KI. The major actions of iodide on thyroid function are inhibition of thyroid hormone release from the thyroid gland and a transient decrease in thyroid hormone synthesis (the acute Wolff-Chaikoff effect). Iodide causes a transient decrease in thyroid hormone synthesis and it also inhibits thyroglobulin proteolysis and release of T4 and T3. Iodide used for treatment of thyroid storm and preoperative preparation for emergency procedure. High-dose iodine in combination with other drugs to treat thyroid storm can be used since iodide can quickly inhibit thyroid hormone release and thyroid hormone synthesis. The suggested dose of oral inorganic iodide for the treatment of thyroid storm is 200–2000 mg per day. Used for potential treatment of Graves' disease. Oral cholecystographic agents (sodium iopanoate and sodium ipodate) have also been used for rapidly lowering thyroid hormone levels in combination with MMI74 and may be useful in thyroid storm.

Side effects of iodine-containing compounds

Iodine has a few mild side effects such as drug fever, sialoadenitis, conjunctivitis, mucositis, vasculitis, cutaneous rash, nausea, vomiting, diarrhea, dysuria and only in rare cases, acute renal failure and thrombocytopenia and leukemoid eosinophilic granulocytosis [17,20].

Conclusion

Hyperthyroidism is the most common cause of thyroid dysfunction in areas with mild and moderate iodine deficiency [4]. Occurrences are seen at all ages but presentation peaks between 20 and 50 years of age secondary to the higher prevalence of Graves' disease. Toxic multinodular goiter typically occurs after age 50 years, as opposed to toxic adenoma, which presents at a younger age. All forms of thyroid disease are more common in women. Amiodarone-induced hyperthyroidism (AIH) is much more common and challenging to treat than amiodarone-induced hypothyroidism. Amiodarone-induced thyrotoxicosis results from two different mechanisms. The iodine released during the metabolism of the drug is responsible for the thyrotoxicosis in most cases. Many of the symptoms of hyperthyroidism such as sweating, anxiety, tremor and palpitations are caused by increased sympathetic activity and can be controlled rapidly by beta blockers. Propranolol in relatively high doses of over 160 mg per day can mildly inhibit conversion of T4 to T3.

Acknowledgments

The author would be grateful to anonymous reviewers by the comments that increase the quality of this manuscript.

Data Sources: Sources searched include Google Scholar, Research Gate, PubMed, NCBI, NDSS, PMID, PMCID, Scopus database, Scielo and Cochrane database. Search terms included: definition, causes, pathophysiology and management of hyperthyroidism.

References

1. Taylor et al. Global epidemiology of hyperthyroidism and hypothyroidism. Nature Reviews Endocrinology. 2018; 14: 301-316.
2. Uberti ED, et al. Iodine Excess and Hyperthyroidism. Thyroid. 2001; 11: 5.
3. Devereaux D, et al. Hyperthyroidism and thyrotoxicosis. Emerg Med Clin N Am. 2014; 32: 277-292.
4. M Abraham-Nordling, et al. Incidence of hyperthyroidism in Sweden. European Journal of Endocrinology. 2011; 165: 899-905.
5. Casey et al. Subclinical Hyperthyroidism and Pregnancy Outcomes. Obstet Gynecol. 2006; 107: 337-341.
6. Venkat et al. Hepatic Dysfunction in Hyperthyroidism. Gastroenterology & Hepatology. 2011; 7.
7. Franklyn J. Thyrotoxicosis. Clinical Medicine. 2003; 3: 11-15.
8. De Leo S, Lee SY, Braverman LE. Hyperthyroidism. Lancet. 2016; 388: 906-918.
9. Léger J et al. Hyperthyroidism in Childhood: Causes, When and How to Treat. J Clin Res Pediatr En docrinol. 2013; 5: 50-56.
10. Vitti P, Rago T, Tonacchera M, Pinchera A. Toxic multinodular goiter in the elderly. J Endocrinol Invest. 2002; 25: 16-18.
11. Pearce EN, Farwell AP, Braverman LE. Thyroiditis. N Engl J Med. 2003; 348: 2646-2655.
12. Martino E, Bartalena L, Bogazzi F, Braverman LE. The effects of amiodarone

on the thyroid. Endocr Rev. 2001; 22: 240-254.

13. Lee SY et al. A review: Radiographic iodinated contrast media-induced thyroid dysfunction. J Clin Endocrinol Metab. 2015; 100: 376-383.

14. Fumarola A et al. Medical Treatment of Hyperthyroidism. Exp Clin Endocrinol Diabetes. 2010.

15. Roy G, Mugesh G. Bioinorganic chemistry in thyroid gland: effect of antithyroid drugs on peroxidase-catalyzed oxidation and iodination reactions. Bioinorg Chem Appl. 2006; 23214.

16. Koenig RJ. Regulation of type 1 iodothyronine deiodinase in health and disease. Thyroid. 2005; 15: 835-840.

17. Abraham and Acharya. Current and emerging treatment options for Graves' hyperthyroidism. Therapeutics and Clinical Risk Management. 2010; 6: 29-40.

18. Cooper D. Antithyroid drugs. N Engl J Med. 2005; 352: 905-917.

19. Erem et al. Radioiodine Treatment of Hyperthyroidism. Endocrine. 2004; 25: 55-60.

20. Suwansaksri N et al. Nonthionamide Drugs for the Treatment of Hyperthyroidism: From Present to Future. International Journal of Endocrinology. 2018; 2018: Article ID 5794054.

21. Kaykhaei MA et al. Low doses of cholestyramine in the treatment of hyperthyroidism. Endocr. 2008; 34: 52-55.