

Thyroid Disease — Part 1

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GOALS AND OBJECTIVES

Goals:

To provide the pharmacist with information regarding hypothyroidism and hyperthyroidism & their symptoms, signs, diagnosis and etiologies.

Objectives:

After completing this article, the pharmacist should be able to:

1. List the major signs and symptoms of hypothyroidism and hyperthyroidism.
2. Discuss the diagnostic procedures involved with hypothyroidism and hyperthyroidism.
3. Describe the major causes of hypothyroidism and hyperthyroidism.
4. Discuss the primary laboratory procedures associated with hypothyroidism and hyperthyroidism.

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Introduction

Hypothyroidism and hyperthyroidism are common diseases of the thyroid gland which affect about 1% to 4% of the population in the United States. Females account for 75% of the thyroid disorders. The primary form of treatment for these chronic disorders is pharmacological intervention. Consequently, the pharmacist is often the health professional that can optimize patient care by appropriate counseling, detecting adverse effects and potential drug interactions, and participating in the selection and evaluation of drug therapy.

The Thyroid Gland

The thyroid gland is located on top of the trachea and is a highly vascular organ which consists of two lobes connected by a middle section known as the isthmus. The thyroid gland aids in the regulation and maintenance of normal body metabolism, homeostasis and development. The thyroid gland is responsible for synthesizing, storing and releasing triiodothyronine (T_3 ; half-life = 1.5 days) and thyroxine (T_4 ; half-life - 7 days), which are active hormones.

The activities involved with these processes occur via a complex negative feedback mechanism involving the thyroid gland and the hypothalamic-pituitary axis. The negative feedback mechanism is associated with changing levels of thyroid hormone. Low circulating levels of thyroid hormone initiate the release of TSH (thyroid stimulating hormone) from the pituitary and appear to influence the secretion of TRF (thyrotropin releasing factor) from the hypothalamus. These increased levels of TSH enhance increased iodide trapping by the gland which eventually results in an increase in synthesis and circulating thyroid hormone levels. As the thyroid hormone levels increase, the pituitary and hypothalamic centers impede release of TRF and further thyroid hormone biosynthesis. As thyroid hormone levels decrease, the process is repeated.

Both T_4 and T_3 synthesis occur in the thyroid gland, while T_3 production also occurs as a result of monodeiodination of secreted T_4 . After the dietary inorganic iodide is trapped by the

gland, it is rapidly converted to iodine and incorporated with tyrosine molecules to form monoiodotyrosine (MIT) and diiodotyrosine (DIT). Combinations of these molecules (i.e., DIT and MIT; DIT and DIT) form T_3 and T_4 . These hormones are highly protein bound in the circulation. Only 0.2% of T_3 and 0.02% of T_4 are in the unbound form and active.

Diagnostic Procedures

A variety of diagnostic procedures have been developed to evaluate thyroid function as well as aid in the diagnosis of thyroid disorders. Several laboratory tests can assess thyroid homeostasis and metabolic function. These tests evaluate circulating hormone levels, glandular activity, hypothalamic-pituitary function, autoimmunity, and various nonspecific metabolic indices. Initial screening tests for thyroid disorders should include the resin triiodothyronine and thyroxine uptake and the free thyroxine index (FT₄I). If hypothyroidism is suspected, then a thyroid stimulating hormone (TSH) level as well as antibodies to thyroglobulin and the microsomal antigen should be assessed. Conversely, triiodothyronine by RIA and the thyrotropin releasing hormone (TRH) are of significant value in determining the presence of hyperthyroid state. Antibodies confirm the presence of an autoimmune thyroid disorder, while radioactive iodine uptake (RAIU) and thyroglobulin values are useful in evaluating a malignancy and nodular disease.

A variety of nonspecific tests are associated with thyroid function. Serum cholesterol, carotene, lactic dehydrogenase, and creatine phosphokinase levels may be decreased in individuals with hyperthyroidism and elevated in those with hypothyroidism.

In addition, to thyroid function tests, an evaluation of individuals for thyroid disorders must include an examination of the thyroid gland to indicate any abnormalities (i.e., enlargement, nodules) as well as an examination of other organ systems to assess any effects associated with thyroid hormone functions. In addition, a complete history, including any symptoms related to thyroid hormone functions, history of

neck symptoms, family history of thyroid dysfunction, and/or a history of any chest or neck irradiation as a child, must be completed.

As indicated, the thyroid gland is very complex and is associated with many normal physiological functions. The wide variety of complex thyroid function tests are very beneficial, but can be affected by other factors (i.e., drugs, diseases). For example, starvation, acute depression, and chronic disorders affecting major organs may be associated with the appearance of thyroid dysfunction as indicated by thyroid function tests. However, thyroid hormone supplementation is usually not needed and may cause harm. In most of these situations, the reversal of apparent thyroid abnormality is associated with a control of normal physiological processes. Tables I and II provide information regarding some thyroid function tests and the drugs that alter them.

Symptoms of Hyperthyroidism

Hyperthyroidism or thyrotoxicosis is characterized by increased metabolism of all body systems which can be attributed to excessive quantities of thyroid hormone. The symptoms include muscle weakness, fatigue, palpitations, nervousness, insomnia, flushing, diarrhea, abnormal menstrual flow, and weight loss despite increased appetite. These symptoms are reflective of increased physiological effects.

However, not all symptoms will be present in each patient. In some patients, particularly the elderly with chronic disease, many of the typical symptoms will not be present, but other symptoms such as low grade fever, delayed speech and congestive heart failure will obscure the diagnosis. This disorder is known as masked hyperthyroidism. If this problem is not treated, coma and death can occur.

Causes of Hyperthyroidism

Although the primary features of excessive production of thyroid hormone and accelerated metabolism are common to hyperthyroid states, thyrotoxicosis is a disorder of multiple etiologies.

Gravesø disease or toxic diffuse goiter is characterized by symptoms of hyperthyroidism, a

diffusely enlarged goiter, infiltrative ophthalmopathy, dermopathy and acropathy. All of these findings may not be present for any one case. The exact cause of Gravesø disease is unknown, but it is primarily a disease of females, the average age of occurrence is between 30 and 40 years, it has a familial association and stress appears to be a factor in its occurrence.

Many of the underlying factors appear to have an autoimmune component involving both humoral and cellular mechanisms. The diagnosis of Gravesø disease is confirmed by elevated levels of various laboratory parameters, such as T₃ and T₄ and RAIU. In addition, antibodies are present in approximately 80% of patients with Gravesø disease.

The thyroid gland in Gravesø disease is frequently diffusely enlarged and symmetric, with a firm but rubbery consistency. Thrills (a vibration felt on palpitation) and bruits (a sound heard in auscultation) may be found in the hyperfunctioning goiter. Bruits are more common and may be found over the entire gland. Both will disappear as a euthyroid state is reached.

Ocular manifestations vary from the characteristic infiltration ophthalmopathy of Gravesø disease to the noninfiltrative. The noninfiltrative ocular problems result from hyperactivity of the sympathetic system and can be found in any thyrotoxic condition. They are usually reversible with control of the thyrotoxicosis. The infiltrative ocular findings are the most obvious in Gravesø disease. They may be unilateral or bilateral and may not be reversible. Edema and swelling, photophobia, and conjunctivitis are common problems. Protrusion of the cornea more than normal (proptosis) results in a wide-eyed staring expression. Blindness resulting from venous congestion and hemorrhage of the retina and optic nerve can occur. Ocular symptoms occur in approximately half the patients, while only five percent have severe problems.

Pretibial myxedema is an uncommon mucopolysaccharide infiltration of the skin which

results in cutaneous thickening and pigmentation over the tibial aspects of the leg. Although usually asymptomatic, this dermatopathy can be treated with a topical corticosteroid.

The least common of the major causes of hyperthyroidism is toxic nodular disease or Plummer's disease. It is characterized by an autonomous hyperfunctioning nodule of approximately five centimeters in diameter which produces larger than normal doses of hormone and suppression of normal thyroid tissue. This etiology is more common in patients in their fifth or sixth decade of life and is the most common form in the elderly. The nodule(s) may remain asymptomatic for many years. However, toxicity can occur in the later years.

Subacute thyroiditis is an inflammatory condition of the thyroid that is believed to have a viral etiology. The symptoms are very similar to a viral infection and include malaise, flu-like symptoms and fever as well as localized swelling of the gland and hyperthyroidism or hypothyroidism symptoms. Typically, conditions associated with hyperthyroidism occur initially, but chronic inflammation eventually results in hypothyroidism features. Subacute thyroiditis is usually self-limiting and treatment consists of symptomatic measures (i.e., heat, rest, analgesics).

Triiodothyronine toxicosis is characterized by normal levels of thyroxine and elevated levels of triiodothyronine. It is associated with Graves' disease, toxic goiters, and carcinomas. Elevated levels of triiodothyronine often precede elevated thyroxine levels.

Iatrogenic thyrotoxicosis has occurred with chemicals. Iodine has caused thyrotoxicosis in individuals who live in iodine deficient areas, then receive iodine supplementation. This has been the most common mechanism associated with iodine, but thyrotoxicosis has occurred in individuals following injection of radio contrast material. Lithium acts similarly to iodine in preventing hormone release. Consequently, hyperthyroidism can occur after its withdrawal. Amiodarone contains large amounts of iodine

and has been implicated in hyperthyroidism. This appears to be related to the iodine content rather than any pharmacological activity.

Hypothyroidism or myxedema is a state characterized by a decrease in all body processes because of a lack of thyroid hormone. The clinical features of hypothyroidism are often obscure and nonspecific. They include weight gain despite limited intake, decreased sweating, fatigue, mental and physical sluggishness, constipation, cold intolerance, muscle aches, and tingling. In addition, diminished sympathetic tone may lead to drooping of the eyelids, delayed deep tendon reflexes, dry brittle hair and nails, and cool, coarse skin.

Since the conversion of carotene to vitamin A is impeded in hypothyroidism, a yellowish tint may be present on the palms of the hands. Both cardiovascular and neurological manifestations indicate a slowing or low output effect. The former may appear as angina or congestive heart failure, while the latter may be reflected in ECG findings.

Although renal disease is not apparent, alterations in renal function, such as changes in antidiuretic hormone secretion and glomerular filtration rate, may occur. A comparison of the clinical features associated with hyperthyroidism and hypothyroidism appears in Table III.

Hypothyroidism can be goitrous or nongoitrous. The goiters or enlargements of the thyroid result from excessive thyroid stimulating hormone activity in response to reduced thyroid levels. Goitrous hypothyroidism disorders include endemic, multinodular, drug induced, dysmorphogenesis, and Hashimoto's thyroiditis, while non-goitrous conditions are caused by cretinism, iatrogenic and idiopathic atrophy, and secondary hypothyroidism of pituitary or hypothalamic origin.

Pituitary hypothyroidism can occur as a result of trauma, pituitary tumors or other diseases associated with abnormal pituitary gland function. Hypothalamic hypothyroidism appears to be a rare disease which results in part from inadequate thyrotropin releasing factor secretion.

A common cause of hypothyroidism is associated with therapy for hyperthyroidism. Iatrogenic hypothyroidism occurs in some of the patients receiving radioactive iodine and/or surgery.

Iodopathic atrophy of the thyroid gland appears to be associated with antibodies involved in a destructive immune process.

Cretinism or congenital hypothyroidism is attributed to an in utero deficiency of thyroid hormone or may result from defective hormone synthesis, incomplete development of the thyroid gland, or pituitary or hypothalamic dysfunction in the newborn. The clinical features vary with regard to the amount, age of onset, and duration of thyroid hormone deficiency. The initial features include prolonged jaundice, constipation, drooling, hypothermia, a heavy expression, umbilical hernia, hoarseness, and a protruding abdomen. After three to six months, poor appetite, growth retardation and development, and failure to thrive become more apparent. However, neurological damage may already be irreversible. In many cases, an early recognition of the problem may be possible by a radioimmune assay of thyroid stimulating hormone in cord blood.

Endemic goiter is the general term used to describe thyroid enlargement associated with iodine deficiency which is encountered in a significant amount of the population. As with other thyroid diseases, females are affected more frequently than males. The quantity of dietary iodine will usually determine the degree of enlargement which becomes nodular with advancing years.

Goiters may occur as a result of drug use. Drugs used to treat hyperthyroidism, such as iodides or thioamides, may cause goiter if excessive doses are employed. Lithium has been implicated as a goitrogen when administered to individuals with abnormal glands. This effect may appear after several months to several years of therapy. If the disease is treated with thyroxine (T_4) or lithium is discontinued, the goiters usually respond.

The tricyclic antidepressants (i.e., imipramine) have also been associated with the development of goiter. Tolbutamide has been shown to inhibit iodide binding which can result in a reduction of thyroid hormone. Dietary goitrogens, such as cabbage, normally do not produce any significant degree of hypothyroidism unless large quantities are consumed for long periods of time.

Dyshormonogenesis refers to a specific group of familial thyroid disorders which are associated with abnormalities in synthesis, delivery, or peripheral action of thyroid hormones. These disorders can result from a variety of impairments (i.e., lack of converting enzyme, impaired release processes) and are detected primarily by elimination of other causes.

Chronic thyroiditis or Hashimoto's thyroiditis is characterized by diffuse enlargement and lymphocytic infiltration of the thyroid, an immunological abnormality and hypothyroidism. It is a frequent cause of hypothyroidism and is 10 to 20 times more common in females, with the middle ages the peak for occurrence. Like Graves' disease, there appears to be familial factors involved in its development. Evidence indicates that many of the major factors and processes associated with Hashimoto's thyroiditis have an autoimmune basis or component.

Table 1
Examples of Thyroid Function Tests

Tests	Hyperthyroidism	Hypothyroidism
Protein Bound Iodine (PBI)	Increase	Decrease
Thyroxine (T ₄)	Increase	Decrease
Resin Triiodothyronine Uptake (RT ₃ U)	Increase	Decrease
Thyroxine Uptake (RT ₄)	Increase	Decrease
Free Thyroxine Index (FT ₄ I)	Increase	Decrease
Triiodothyronine (T ₃)	Increase	Decrease
Free Triiodothyronine Index (FT ₃ I)	Increase	Decrease
Radioactive Iodine Uptake (RAIU)	Increase	Decrease
Thyrotropin Stimulating Hormone (TSH)	Decrease	Increase
Triiodothyronine Suppression Test	Nonsuppression	Nonsuppression
Thyrotropin Releasing Hormone Test (TRH)	No response	Response
Thyroid Scan	Enlarged	Hypofunction

Table 2
Examples of Drugs Which May Affect Thyroid Function Test

Drugs	Suspected Mechanism
Estrogens Oral Contraceptives Clofibrate	Increase serum thyroxine Binding Globulin (TBG) concentrations
Anabolic Steroids Danazol Glucocorticoids	Decrease Serum TBG Concentrations
Phenylbutazone Mitotane Chloral Hydrate 5 - FU	Displacement of T ₄ and T ₃ from TBG
Tincture of Iodine SSK I Lugol's Solution Iodide Compounds	Dilute Total Body Iodide Pools
Furosemide Ethacrynic Acid	Decrease Total Iodide Pools
Phenobarbital	Hepatic Enzyme Induce of T ₄ Metabolism
Amiodarone	Impair Conversion of T₄ to T₃

Table 3
Clinical Features Associated With Hyperthyroidism & Hypothyroidism

Feature	Hypothyroidism	Hyperthyroidism
Hair	Dry, brittle, sparse	Thinning, fine texture
Eyes	Ptosis, Edematous eyelids	Prominence of the eyes
Temperature	Cold intolerance	Heat intolerance
Weight	Weight gain despite decreased appetite	Weight loss despite increased appetite
Cardiac	Cardiac enlargement, low output CHF	Palpitations, High output CHF
Emotional	Depressed; lethargic; increased sleep needs	Nervous, irritable, insomnia
Neuromuscular	Delayed deep tendon reflexes	Rapid deep tendon reflexes
Gastrointestinal	Constipation	Diarrhea
Genitourinary	Dysmenorrhea, Menorrhagia	Amenorrhea, decreased length of menstrual flow
Extremities	cold and dry skin	hot and moist skin