Chapter 3: Thyroid Disorders: A Comprehensive Review

10 Contact Hours

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Learning objectives

- Describe the epidemiology of thyroid diseases
- Define the etiology and pathophysiology of thyroid diseases
- Recognize the most common signs and symptoms of subclinical thyroid disease versus symptomatic thyroid diseases
- Distinguish between hyperthyroidism and hypothyroidism
- Characterize the signs and symptoms present in the progression of thyroid diseases
- Identify and describe the effectiveness of the diagnostic tests and criteria used to diagnose thyroid diseases
- Identify neurological manifestations of thyroid diseases
- Evaluate the various non-surgical treatment options of thyroid diseases
- Discuss various lifestyle modifications for patients with uncomplicated thyroid disease
- Describe pharmacologic treatment options for thyroid diseases (i.e. levothyroxine, radioactive iodine, propylthiouracil, etc.)
- Describe pharmacological and non-pharmacologic treatment approaches to pregnant patients
- Describe the effectiveness of monitoring disease progression of thyroid diseases
- Develop optimal treatment plans for individual patients with thyroid diseases based on symptomology and severity of disease
- Describe new advancements in treatment options and early detection of thyroid disorders
- Differentiate between benign and metastatic thyroid nodules
- Design methods for educating patients on the regimens that improve patient compliance and prognostic outcomes.

Needs assessment information

Thyroid disorders commonly affect women and geriatric patients. The resulting complications from undiagnosed and untreated forms of thyroid diseases are implicated in pregnancy fatalities, cardiovascular complications and metabolic syndrome. The fundamental approach to the prevention, diagnosis, pharmacologic and non-pharmacologic treatment of patients with various forms of thyroid diseases is constantly evolving. Early detection and treatment equates to better patient outcomes and overall prognosis. Effective management encompasses patient awareness and education, promotion of lifestyle modifications, treatment adherence and constant monitoring of the disease progression. Despite these well-established principles, under- and overtreatment remain common. Physicians and other healthcare professionals can exert dramatic difference in treatment success by involving the patient personally in the treatment choices, instead of being regarded merely as passive recipients of therapy. Moreover, they are well positioned to correct therapeutic shortcomings by identifying and managing common factors that affect patient compliance to therapy and monitoring, effects of common comorbid conditions, surgery, and concomitant medications and in the process improve overall therapeutic outcome and quality of life.

Introduction

Two of the most common thyroid diseases were named after their discoverers, Graves and Hashimoto. The historical background of the thyroid gland provides the foundation necessary to understand areas of modern endocrinology such as hormone replacement therapy, feedback mechanisms, and the use of radioactive isotopes.

Goiter, or an enlarged thyroid gland, was already recognized as a medical problem long before the discovery of the organ involved. Its visible protrusion at the neck was a subject of many ancient medical reports. In fact, historical records show that as early as 1600 BC, the Chinese were already treating goiter with burnt seaweeds. In 15 AD, a scientist named Aurelius Celsius was among the first ancient scientists who clearly described thyroid tumor overgrowths, and provided recommendations as to its treatment including the use of caustics and surgery. It was also around this era that Gaius Plinius incorrectly linked goiter with the consumption of dirty drinking water, referring to the epidemics of goiter in the Alps, and also suggested burnt seaweed as treatment (1).

During the Greco-Roman period, another prominent scientist, Gallen, incorrectly proposed the function of the thyroid gland as a secretory lubricating organ for the larynx. Just like the Chinese thousands of years before him, he referred to burnt sponge as treatment for goiter.

In 1656, the word “thyroid”, meaning shield, was given to the small gland on the neck by Thomas Wharton who likened its shape to those of ancient Greek shields. The belief that dirty drinking water caused goiter persisted for a long time, through to the Renaissance period, until the discovery of iodine in the burnt seaweed at the start of the 19th century in Paris. Its discoverer, Bernard Courtois oxidized kelp using sulfuric acid to obtain the substance, iodine, meaning “violet”. Its discovery led to its universal adoption as a treatment agent for goiter. The years succeeding its discovery made way for better understanding of the disease, most notably the link between palpitations, exophthalmoses and the enlarged thyroid gland. In 1909, E.T. Kocher was awarded the Nobel Prize for his work on the thyroid gland, most notably for introducing its surgical removal, a technique now known as thyroidectomy (1).
Definition of terms

Thyroid gland – it is an endocrine gland that is anatomically situated in the lower front of the neck. Its main function is to make thyroid hormones, which are secreted into the blood and then carried to every tissue in the body. Thyroid hormone helps the body use energy, stay warm and keep the brain, heart, muscles, and other organs working as they should (221). The gland varies from an H to a U shape and is formed by 2 elongated lateral lobes with superior and inferior poles connected by a median isthmus, with an average height of 12-15 mm, overlying the second to fourth tracheal rings. The isthmus is encountered during routine tracheotomy and must be retracted (superiorly or inferiorly) or divided. Occasionally, the isthmus is absent, and the gland exists as 2 distinct lobes (220).

Goiter – it refers to the abnormal enlargement of the thyroid gland. It is important to know that the presence of a goiter does not necessarily mean that the thyroid gland is malfunctioning. A goiter can occur in a gland that is producing too much hormone (hyperthyroidism), too little hormone (hypothyroidism), or the correct amount of hormone (euthyroidism). A goiter indicates the presence of a condition that is causing the thyroid to grow abnormally (221).

Hypothyroidism – it is a common endocrine disorder resulting from the deficiency of thyroid hormones (223).

Epidemiology

As of 2009, an estimated 1 percent of the American population has been diagnosed with hyperthyroidism (2). The majority of those diagnosed are adult women, with 12.6 million reported to have received treatment in 2008 (latest data). According to the Household Component of the Medical Expenditure Panel Survey (MEPS-HC), about 23 percent of women over the age of 65 received treatment for thyroid disease, a significantly high percentage compared to women between 18-44 and 45-64 years of age (3.5 percent and 13.3 percent, respectively). According to the same survey, 12.9 percent of Caucasian non-Hispanic women received treatment in 2008, while their Hispanic and black counterparts only accounted for 6.2 percent and 5.1 percent of the overall treatment rate, respectively. In terms of healthcare costs, a total of $4.3 billion was spent on various treatments for thyroid diseases with emergency department visits and prescription medications accounting for $2.2 billion and $1.4 billion of it, respectively. The average American woman with thyroid disease spent $409 yearly in treatments (3).

In the US, Graves disease or diffuse toxic goiter is the most commonly diagnosed hyperthyroidism followed by Plummer’s disease and toxic adenoma. Graves disease accounted for 60-80 percent of the diagnosed cases while 15-20 percent and 3-5 percent accounted for Plummer’s disease and toxic adenoma, respectively. Plummer’s disease is less prevalent because of the sufficient iodine found in the American diet. However, Plummer’s disease is the most common cause of hyperthyroidism in elderly individuals and in areas of endemic iodine deficiency (4).

Approximately 4.6 percent of the U.S. population over the age of 12 years has primary hypothyroidism (2). This figure is significantly lower than compared to the rest of the world who receive inadequate iodine in their diets. Those few who are diagnosed with hypothyroidism usually have Hashimoto’s thyroiditis, an autoimmune disease, although it is worth noting that not all patients diagnosed with Hashimoto’s thyroiditis develop hypothyroidism. Pregnant women with hypothyroidism are at greater risk for developing preeclampsia, delivering preterm and losing the baby to miscarriage. Secondary and tertiary hypothyroidisms are rare and estimated to occur in 1 out of 80,000 individuals.

Some of the most prevalent and leading life-threatening diseases can be caused by undiagnosed and untreated thyroid disease. In the US and other developed countries, obesity, cardiovascular disease and diabetes are leading causes of death and all three are potentially precipitated by thyroid diseases (5). Thyroid disorders upset the hormonal regulation of metabolic processes, resulting in obesity, diabetes and eventually heart diseases.

Thyroid disorders generally occur because of two abnormalities; dysfunction and abnormal growth of the thyroid gland. Benign nodules are a fairly common serendipitous finding during routine check ups. Sometimes, during physical exams, benign nodules are noted and generally do not pose a serious health concern because the gland’s functional integrity remains intact. Patients with benign nodule growths typically complain of difficulty swallowing and speaking. Thyroid cancers, on the other hand, are rare and can pose serious health problems. They represent approximately 1 percent of new cancer diagnoses each year. Like other forms of thyroid diseases, thyroid cancers are most prevalent in women, especially those over the age of forty. The full recovery rate of thyroid cancer with proper treatment is 90 percent (6).

THE ROLE OF HPT AXIS AND HORMONES

In order to understand the etiology of thyroid diseases, a sound understanding of the hypothalamic pituitary-thyroid (HPT) axis or thyroid homeostasis is crucial.

HPT regulates the serum level of thyroid hormones, triiodothyronine (T3) and thyroxine (T4), in the serum through a feedback mechanism involving several hormones and endocrine organs. The loop begins in the hypothalamicus where the hypothalamic TSH-releasing hormone (TRH) is secreted, then transported to the endocrine cells of the pituitary gland. These cells produce thyroid stimulating hormone (TSH) which when bound to TRH receptors, stimulates the genetic expression of TSH β-subunits. When TSH matures, it is released from the pituitary gland to the thyroid gland, where it stimulates the production and release of T3 and T4 (7). In turn, these two hormones inhibit TRH production through a negative feedback loop mechanism, thus establishing a balance or “set point” that is under tight endocrinological control. For example, when circulating T3 and T4 levels decrease, the pituitary gland increases the production of TSH and if the vice versa happens i.e. T3 and T4 levels increase in the blood, the production of TSH is inhibited. Drugs, radiation, cancers, stress and other factors can upset this balance and lead to either hypothyroidism or hyperthyroidism.

Ultra-short feedback control also plays a role in thyroid hormone regulation. It is a feedback control mechanism within the greater HPT axis negative feedback loop that regulates the release of thyroid hormones via auto-inhibitory actions of TSH in its own secretion without the intermediate actions of an additional hormone.
Functional conditions of the HPT axis

<table>
<thead>
<tr>
<th>Euthyroidism: Normal thyroid activity</th>
<th>Hyperthyroidism: Overactivity of the thyroid gland and inappropriate secretion</th>
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<tbody>
<tr>
<td>Hypothyroidism: Underactivity of the thyroid gland and low secretory capacity</td>
<td>Thyrotoxicosis: Oversupply of thyroid hormones</td>
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Role of hormones

The synthesis and secretion of TRH is mediated by the TRH gene, located on chromosome 3, in the hypothalamus and other endocrine organs such as the brain, pancreatic β-cells, thyrotropic C-cells, myocardium, prostate, testis, spinal cord, epidermal layers and the anterior pituitary gland.

TSH consists of α and β subunits with the former located on chromosome 6 and the latter gene on chromosome 1. It is synthesized and secreted by the thyrotrophs of the anterior pituitary gland. The β subunits determine the biologic specificity, an important function that allows for the binding of TRH with its receptor on the thyrotrophs. Once bound, TSH undergoes glycosylation to become a biologically active molecule that permits its own rapid clearance from the circulation. Mutations in the TSH β gene have been implicated in familial central hypothyroidism.

Thyroid hormone receptors are found in almost all body tissues. T3 is the active form of the two thyroid hormones and directly affects body tissues upon release from the thyroid gland. The pro-hormone T4 undergoes de-iodination in the peripheral tissues to become T3. Thyroid hormones need to be bound with carrier proteins such as the thyroid hormone binding globulin (TBG) so they can be transported. TBG binds with 75 percent and 100 percent of the circulating T4 and T3, respectively. The remaining 25 percent of the circulating T4 binds with thyroxine binding pre-albumin and albumin.

In the past, T4 was considered as the main thyroid hormone. However, recent studies have shown that T3 is actually the primary thyroid hormone, because (79):

- T3 is physiologically four times more active than T4
- T4 is convertible to T3 in the target cells
- T3 has 10 times higher binding specificity to receptors compared to T4
- There are four times more T3 receptors than that of T4

An adequate supply of iodine is needed to maintain normal thyroid hormone production. The daily recommended minimum intake is 150 mcg, with intake of less than 50 mcg frequently linked to the development of goiter. On the other hand, elevated iodine levels inhibit iodide oxidation and organification; excess iodine inhibits thyroglobulin proteolysis, the principal mechanism for the anti-thyroid effect of inorganic iodine in patients with thyrotoxicosis.

The physiological effects of thyroid hormones are mediated by nuclear receptors through gene expression regulation. Thyroid hormones regulate metabolism, brain function and development, respiratory, nervous and cardiovascular systems, homeostasis, muscle strength, skin dryness, menstrual cycles, weight, and cholesterol levels. Their physiological roles are discussed in detail below:

- Brain development and skeletal maturation of the fetus are dependent on both the fetal and maternal thyroid hormone production. Insufficient thyroid hormones can very well lead to mental retardation and dwarfism.
- T3 controls basal metabolism by regulating oxygen expenditure and heat production. Abnormal T3 serum levels result in increased sensitivity to heat and cold in hyperthyroidism and hypothyroidism, respectively.
- T3 exerts several effects on the muscles. It is responsible for the stimulation and inhibition of the genetic transcription of myosin heavy chain alpha and myosin heavy chain beta, respectively, thereby, regulating cardiac muscle contractility. Additionally, T3 stimulates the transcription of calcium ATPase, alters isoforms of sodium-potassium ATPase genes, and increases beta-adrenergic receptors and G proteins levels, exerting an overall positive inotropic and chronotropic effects on the heart.
- Thyroid hormones sensitize the tissues to catecholamine stimulation in hyperthyroid states. This is why beta blockers are a mainstay in patients with hyperthyroidism who present with tachycardia and arrhythmias.
- Thyroid hormones stimulate the GI tract leading to diarrhea in hyperthyroid states and constipation in hypothyroidism.
- Thyroid hormones stimulate bone turnover leading to osteopenia in long-standing hypothyroid condition.
- Thyroid hormones stimulate hepatic metabolic processes such as gluconeogenesis and glycolysis resulting in hyperglycemia in patients with hyperthyroidism.
- Thyroid hormones stimulate cholesterol production and degradation resulting in high serum cholesterol levels in patients with hyperthyroidism.

TYPES OF THYROID DISEASES AND THEIR ETIOLOGY

Thyroid diseases are most often of benign origins. However, there are rare cases where malignant tumors of the thyroid gland and other organs have lead to elevated or decreased levels of serum thyroid hormones. Benign thyroid diseases include nontoxic, benign toxic and inflammatory conditions.

Benign thyroid disorders causing hypothyroidism

As mentioned above, hypothyroidism in the United States and other areas of adequate iodine intake is largely attributed to the autoimmune disease, Hashimoto’s thyroiditis. Just like other thyroid diseases, it is most prevalent in adult women, with its risk of development increasing with age (2).
Primary hypothyroidism

Primary hypothyroidism refers to the underactivity of the thyroid gland, leading to decreased circulating thyroid hormones, despite normal pituitary stimulation by TRH. There are several kinds of primary hypothyroidism depending on their causes, namely; (8):
- Chronic lymphocytic (autoimmune) thyroiditis (Hashimoto’s thyroiditis)
- Postpartum thyroiditis
- Subacute (granulomatous) thyroiditis
- Drug-induced hypothyroidism
- Iatrogenic hypothyroidism

Chronic lymphocytic (autoimmune) thyroiditis or Hashimoto’s thyroiditis

In the US, the single most common cause of acquired hypothyroidism is Hashimoto’s thyroiditis. It is named after its discoverer, Hakaru Hashimoto. The autoimmune disease is characterized by the destruction of thyroid cells by antibodies. Essentially, the body does not recognize the thyroid cells as its own and directs its immune system to attack and destroy them. The result is a chronic immune reaction manifesting as lymphocytic infiltration of the thyroid gland and gradual and steady destruction of its healthy cells. If left untreated, the underactive thyroid gland will produce insufficient thyroid hormones resulting in the slowing down of metabolic processes (8).

Postpartum thyroiditis

Some women who have just given birth are at risk of developing hypothyroidism in the form of postpartum thyroiditis. It is estimated that up to 10 percent of postpartum women may develop the condition within one year of delivery. The risk is compounded in women with comorbid juvenile diabetes mellitus.

Subacute granulomatous thyroiditis

Subacute thyroiditis is a self-limiting inflammation of the thyroid gland that usually follows a recent bout of viral upper respiratory tract infection (URTI). It is also known as de Quervain disease, or de Quervain thyroiditis. It is relatively uncommon and usually affects middle-aged women after resolution of viral infections. The course of the disease is summarized in the table below:

Table 1: Disease course of subacute thyroiditis and their characteristic clinical parameters

<table>
<thead>
<tr>
<th>Clinical Parameters</th>
<th>Hyperthyroidism</th>
<th>Hypothyroidism</th>
<th>Euthyroidism</th>
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<tbody>
<tr>
<td>T4, T3</td>
<td>Increased</td>
<td>Decreased</td>
<td>Normal</td>
</tr>
<tr>
<td>TSH</td>
<td>Decreased</td>
<td>Increased</td>
<td>Normal</td>
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Drug-induced and iatrogenic hypothyroidism

Iatrogenic hypothyroidism may be reversible or irreversible, depending on its cause. If precipitated by treatments that cause permanent thyroid damage such as the use of radioactive isotopes, the condition may become permanent. A study by Williams et al., links iatrogenic hypothyroidism with the development of azotemia after treatment of hyperthyroidism, and reduced survival time in azotemic cats (14). In humans, the use of radioactive I-131 in the treatment of Graves disease is strongly associated with permanent hypothyroidism within 3-6 months after treatment. When the same radioactive iodine is used in the treatment of toxic nodular goiters and thyroid nodules, the incidence of developing hypothyroidism is much lower. This is why patients who were administered with radioactive iodine should be monitored closely and tested for clinical and subclinical manifestations of hypothyroidism months after receiving the last dose (12).

Other causes of iatrogenic hypothyroidism are radiation therapy and thyroidectomy. Radiation therapy for head and neck, breast cancers, or Hodgkin disease lymphoma can result in hypothyroidism. Thyroidectomy almost always leads to thyroid insufficiency or hypothyroidism. Patients who received these treatments need their thyroid function to be monitored closely even months after therapy (12).

If precipitated by drugs that interfere with thyroid function, the condition is usually reversible. There are several drugs that are known to cause hypothyroidism, namely (8):
- Amiodarone
- Interferon-alpha
- Thalidomide
- Lithium
- Stavudine
- Oral tyrosine kinase inhibitors – Sunitinib, imatinib
- Bexarotene
- Perchlorate
- Interleukin (IL)-2
- Ethionamide
- Rifampin
- Phenytoin
- Carbamazepine

A recent study by Fava et al. found significantly low levels of serum 25-hydroxyvitamin-D [25(OH)D] in patients with Hashimoto’s thyroiditis, a finding that suggests a possible correlation between vitamin D deficiency and thyroid disease severity and duration (9).
### Genetics and congenital hypothyroidism

Genetic polymorphisms and mutations can also cause hypothyroidism. According to a study by Denny et al. in 2011, a single-nucleotide polymorphism located near the FOXE1 gene is linked with the likelihood of developing thyroid disease, most especially hypothyroidism. Two other studies published 5 years earlier by Vono-Toniolo et al. and Park et al. found errors in thyroid synthesis are linked to genetic mutations. Moreover, Park et al. have traced back these errors to the inadequate production of the TPO gene (15) (16).

Other genetic mutations have also been linked to the development of hypothyroidism. Genetic studies have pointed to the role of TSHR and PAX8 genetic mutations in congenital hypothyroidism without goiter (17) (18). Mutations in the TSHR gene renders the thyroid gland insensitive to TSH, although it has been observed that patients with these genes have a clinically normal thyroid condition and function despite the increased TSH levels and normal thyroid hormone levels in the blood. Additionally, mutations in the PAX8 gene are attributed to the underdevelopment or completely absent thyroid gland. Another disease caused by a genetic mutation that leads to hypothyroidism is Pendred syndrome. The genetic disorder that causes hearing loss and goiter in children is linked to a mutation in the SLC26A4 gene, which results in the defective organification of iodine (19).

Aside from Hashimoto’s thyroiditis, other autoimmune diseases such as polyendocrinopathy types I and II are also associated with hypothyroidism. These two autoimmune disorders are caused by the genetic mutation of the AIRE gene. Patients with polyendocrinopathy type I usually presents with Addison disease, hypoparathyroidism, and mucocutaneous candidiasis. These patients are also more likely to develop autoimmune thyroiditis and hypothyroidism. On the other hand, patients with polyendocrinopathy type 2 often present with adrenal insufficiency and hypothyroidism (8).

### Iodine deficiency / iodine excess

Iron deficiency is prevalent where the diet does not meet the recommended daily intake of iodine. In fact, outside the US, iodine deficiency is the most common cause of hypothyroidism. When left untreated, it results in hypothyroidism, goiter and mental retardation in infants and children born to mothers who were iodine deficient during their pregnancies (20).

Excess iodine in the body leads to the transient inhibition of iodide organization and thyroid synthesis. As discussed above, certain drugs and treatments such as radiocontrast dyes, amiodarone, and herbal supplements can lead to hypothyroidism. Seaweeds have long been recognized as a treatment source of goiter due to their high iodine content. Healthy individuals handle iodine overload well, without requiring treatments by means of rapid sodium-iodide symporter downregulation. The sodium-iodide symporter shuts down, allowing the reduction of intracellular iodine levels and thyroid hormone secretion to restart. However, patients with abnormal thyroid function do not benefit from the same process. It is worth noting that chronic exposure to excess iodine can lead to sustained hypothyroidism in individuals with compromised thyroid function such as those with autoimmune thyroiditis, subtotal thyroidectomy, or history of radioactive I-131 therapy (21).

Secondary and tertiary hypothyroidism

Secondary or tertiary hypothyroidism results from the insufficient stimulation of the hypothalamic-pituitary axis by TSH. Also known as central hypothyroidism, patients diagnosed with this condition usually has a healthy and intact thyroid gland, with the malfunction occurring either in the pituitary gland (secondary hypothyroidism) or the hypothalamus (tertiary hypothyroidism). Listed below are conditions associated with its development (7):

- Pituitary adenoma
- Tumors impinging on the hypothalamus
- Lymphocytic hypophysitis
- Sheehan syndrome
- History of brain or pituitary irradiation
- Drugs
- Congenital nongoiterous hypothyroidism type 4
- TRH resistance
- TRH deficiency

Neoplastic growth in or around the vicinity of the pituitary gland and hypothalamus exerts mechanical compression on these organs and disrupts normal pituitary secretion of TRH, TSH, or both.

<table>
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<th>Drugs</th>
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<tbody>
<tr>
<td>Phenobarbital</td>
</tr>
<tr>
<td>Aminogluthethimide</td>
</tr>
<tr>
<td>Sulfinxozazole</td>
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<tr>
<td>p - aminosalicylic acid</td>
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<td>Ipilimumab</td>
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Lymphocytic hypophysitis causes the enlargement of the pituitary gland and appears as an overall pear-shaped mass in imaging studies. The clinical manifestations of lymphocytic hypophysitis mimics pituitary adenoma, causing symptoms such as headache, nausea, fatigue, hypopituitarism, and diabetic insipidus (22).

Postpartum hypopituitarism or Sheehan syndrome is the ischemic necrosis of the pituitary gland that occurs after severe hemorrhage during or after delivery. The condition is most common in underdeveloped countries and rare in developed countries. Patients with central hypothyroidism resulting from Sheehan syndrome usually present with low ft3 and ft4 but normal or sometimes slightly elevated serum TSH. When given TRH, they exhibit severely blunted TSH responses accompanied by insignificant elevation in serum TSH or ft4 levels after sustained TRH infusion. The elevated serum TSH is due to the increased sialylation which decreases its metabolic clearance and increases its half-life. These patients also have abnormal sleeping patterns (23).

Brain irradiation treatments can result in pituitary deficiency. The severity of hormonal deficiencies is dependent on dose and follow-up duration. In 90 percent of children, the initial dysfunction seen is the compromise of the somatotrophic function, largely manifesting as growth retardation 10 years after radiotherapy. Other endocrine dysfunctions may follow, such as the occurrence of primary thyroid deficiency. In adults, growth hormone deficiency is uncommon.

Drugs such as dopamine and corticosteroids result in decreased TSH secretion. Steroids modulate TSH secretion via the inhibition of the basal, TRH-stimulated TSH serum concentration, and blockade of the normal nocturnal increase in TSH production. Dopamine, on the other hand, blocks the release of TSH via inhibition of the D2 receptors from the pituitary gland. This is seen in the reversal of the blockade and resulting elevated TSH levels following administration of dopamine receptor antagonists such as domperidone and metoclopramide. However, studies have not shown negative effects on TSH secretion with long term therapy of these drugs.

Patients born from consanguineous unions are at an increased risk of developing congenital nongoiterous hypothyroidism type 4. The disorder is caused by a mutation in the TSHB gene. Lab findings usually show low TSH level that does not rise with administration of TRH (24).
Another genetic mutation, this time in the TRHR gene, causes pituitary resistance to TRH. It is an autosomal recessive disorder with no obvious symptoms at birth. Patients with this gene exhibit hypothyroidism accompanied by insensitivity to thyrotropin secretion. The clinical signs and symptoms are often subtle and often do not develop until infants reach several months of age. When they do appear, the first signs include reduced activity and increased sleep, feeding difficulties and GIT problems, prolonged jaundice, myxedematous facies, large posterior fontanels, macroglossia, distended abdomen with umbilical hernia, and hypotonia. Additionally, there is no apparent goiter. Perhaps the two most obvious signs are the slow growth and overall developmental delay of these infants (25).

A mutation in the TRH gene causes TRH deficiency. A recorded case of a girl with congenital TRH deficiency showed positive outcomes with oral TRH therapy (26).

Benign thyroid disorders causing hyperthyroidism

Hyperthyroidism refers to an overactive thyroid gland while thyrotoxicosis refers to elevated levels of thyroid hormones in the blood. Both terms are used interchangeably. As mentioned above, the most common form of hyperthyroidism is Graves disease followed by Plummer disease and toxic adenoma.

Genetic mutations

Just like hypothyroidism, genetic mutations are also implicated in the development of hyperthyroidism. For example, McCune-Albright syndrome, caused by GNAS mutations, causes a variety of endocrine dysfunctions such as hyperthyroidism, precocious puberty, Cushing’s syndrome, and acromegaly (27).

There are several other genetic disorders that cause TSH receptor gene mutations, leading to hyperthyroidism, namely;
- Familial gestational hyperthyroidism
- Transient nonautoimmune hyperthyroidism
- Congenital nongoiterous thyrotoxicosis
- Toxic thyroid adenoma with somatic mutation

Studies have found that women who developed familial gestational hyperthyroidism exhibited elevated serum levels of human chorionic gonadotropin hormone (hCG). Normally, hCG stimulation of the thyroid gland during early pregnancy is expected because TSH and hCG closely resemble each other’s structures, allowing their receptors to accommodate both hormones (28). Another type of hyperthyroidism that occurs in the first trimester is transient nonautoimmune hyperthyroidism. As the name suggests, the condition resolves by itself. Clinically speaking, women who are diagnosed with this condition have hyperthyroidism but do not present with laboratory evidence of thyroid autoimmunity or signs and symptoms consistent with Graves disease. Instead, they may present one or many of the following clinical manifestations (29):
- Normal pregnancy
- Mild nausea and vomiting
- Hyperemesis gravidarum
- Twin or multiple pregnancies
- Mutation in the TSH Receptor
- Hyperplacentosis

Graves disease

The most common cause of hyperthyroidism is Graves disease. Graves disease, also known as toxic diffuse goiter, is an autoimmune disorder characterized by the presence of circulating common autoantibodies (autoimmune antibodies) and anti-TPO and anti-TG antibodies against TSHR. Unlike other autoantibodies which inhibit the normal biological functions of the affected organs, these autoantibodies stimulate the receptor to synthesize and secrete excess T3 and T4. The most significant of these autoantibodies is the thyroid stimulating immunoglobulin (TSI) which binds with the TSHR and exerts agonistic-like effects. As a result, Graves disease is characterized by these three clinical manifestations (33):
- Enlarged thyroid gland (goiter)
- Exophthalmos (protruding eyes)
- Infiltrative dermopathy and ophthalmopathy
- High radioactive iodine uptake

Exophthalmos in Graves disease is thought to be a result from the attack of inflammatory cells on the orbital fibroblasts and fat. The symptom can occur before the onset of hyperthyroidism or be 20 years delayed, with its progress and decline independent of the clinical course of hyperthyroidism. Typical ophthalmopathy in the presence of normal thyroid function is called euthyroid Graves disease. Thyroid hormone levels can be highly elevated in Graves disease. Just like other autoimmune thyroid diseases (e.g. Hashimoto’s thyroiditis), Graves disease is associated with other autoimmune diseases, such as pernicious anemia, myasthenia gravis, vitiligo, adrenal insufficiency, celiac disease, and juvenile diabetes mellitus (33).
Subacute thyroiditis

The second most common cause of hyperthyroidism is subacute thyroiditis, accounting for approximately 15-20 percent of diagnosed cases. Unlike Graves disease, this inflammatory thyroid disease does not result from excessive synthesis of thyroid hormone, rather, it results from the destructive changes to the thyroid gland and subsequent inappropriate release of preformed thyroid hormone. Patients with this disease can expect hypothyroidism to follow (33).

Toxic solitary or multinodular goiter

Toxic multinodular goiter or Plummer disease is the least common form of hyperthyroidism, accounting for only approximately 10-20 percent of diagnosed cases. Its incidence is higher in elderly individuals with chronic goiter. It has been proposed that gene mutations are responsible for the slow but steady thyroid activation that occurs over time. As a result, elevation of thyroid hormone is slow and may only appear to be mildly elevated at the time of diagnosis. Patients with this type of thyroid disease have none of the autoimmune clinical symptoms and lab findings such as circulating antibodies found in patients with Graves disease. They are usually asymptomatic, with their condition being serendipitously found during routine screening. Additionally, because of the autonomous hyperfunctional nature of the nodules, toxic solitary and multinodular goiters usually do not remit (34).

Because of only mild elevations of thyroid hormones, the signs and symptoms of hyperthyroidism due to toxic solitary and multinodular goiters do not set off alarm bells until the patient has already developed complications. However, when these patients are exposed to iodinated radiocontrast or administered amiodarone, the elevated thyroid hormone levels become more pronounced.

Toxic adenoma

Toxic adenoma refers to the benign monoclonal nodular growth which results in autonomous hyperfunctioning of follicular thyroid cells. It is a very rare form of hyperthyroidism, accounting for only approximately 2 percent of the diagnosed cases. The excess thyroid hormones produced inhibits TSH production and secretion (35).

Aside from toxic adenoma and toxic solitary and multinodular goiters, other forms of benign thyroid growths will be discussed in the succeeding pages.

Other causes of hyperthyroidism are rare, namely; metastatic thyroid cancer, struma ovarii, iodide-induced thyrotoxicosis, and molar hydatidiform pregnancy.

Struma ovarii

Struma ovarii is a very uncommon ovarian tumor, accounting only for 1 percent of all ovarian tumors. It is characterized by the presence of approximately fifty percent of thyroid tissue of the overall mass. It secretes excessive thyroid hormones, causing hyperthyroidism (37).

Excess iodine intake

Population surveys have found that residents of geographic locations where the iodine deficiency is high who move to areas of sufficient iodine intake are at greater risk of developing hyperthyroidism. Additionally, there is evidence that points to iodine as a potential immune stimulator that precipitates autoimmune thyroid disease and acts as a substrate for additional thyroid hormone synthesis.

Iodide-induced thyrotoxicosis also occurs in patients with multinodular goiter or autonomous nodule. Iodide-induced thyrotoxicosis or Jod- Basedow syndrome is a frequent occurrence in patients who underwent radiologic treatment or studies using iodine-containing contrast agents. The condition most likely results from the inability of the thyroid gland to cope with iodide excess. It is easily treated with cessation of the excess iodine administration accompanied followed use of anti-thyroid medications. Usually, after elimination of the excess iodine from the body, normal thyroid function returns to pre-exposure levels (33).

Drug-induced hyperthyroidism

The antiarrhythmic drug amiodarone is rich in iodine and structurally resembles the thyroid hormone, T4, and stimulates its receptors. The recombinant protein drug, interferon-alpha may also induce thyroiditis with hyperthyroidism and other thyroid disorders (33).

hCG-induced hyperthyroidism

As discussed previously, hCG also stimulates TSH receptors. Patients with a molar pregnancy, choriocarcinoma and hyperemesis gravidarum produce extremely high levels of serum beta human chorionic gonadotropin (β-hCG), a weak agonist of the TSH receptor. The elevated levels of hCG are especially pronounced during the first trimester of pregnancy but subsides quickly as the pregnancy progresses, usually when the molar pregnancy is evacuated, the choriocarcinoma is managed, and hyperemesis gravidarum resolves by itself (33).

Malignant thyroid diseases

Malignancy is also a possible cause of hyperthyroidism, although it is a rare occurrence in the US. It commonly manifests as a painless, palpable, solitary thyroid nodule. Thyroid cancer may spread to the lymph nodes, lungs, bone and sometimes brain. There are also instances where the growth is localized to the neck region, also referred to as locally advanced cancer, affecting primarily the trachea, esophagus, blood vessels, muscles, or nerves (36). There are several forms of thyroid cancer, namely (38):

- Papillary carcinomas
- Follicular carcinomas
- Medullary thyroid carcinomas (MTCs)
- Anaplastic carcinomas
- Primary thyroid lymphomas and,
- Primary thyroid sarcomas

These carcinomas primarily arise from the two types of cells in the thyroid gland, namely:

- Endodermally-derived follicular cell gives rise to papillary, follicular, and probably anaplastic carcinomas.
- Neuroendocrine-derived calcitonin-producing C cell gives rise to MTCs. Thyroid lymphomas arise from intrathyroid lymphoid tissue, whereas sarcomas likely arise from connective tissue in the thyroid gland.
Papillary carcinoma

Papillary carcinoma is the most common form of all thyroid neoplasms. Exposure to radiation has been strongly linked to increased risk for papillary thyroid carcinoma. This finding is backed by historical data that spans more than 50 years of populations affected by well known nuclear explosion and accidents, namely the Chernobyl plant accident and atomic bombings of Hiroshima and Nagasaki. Additionally, retrospective studies have found that patients who received low-dose radiation therapy for benign tumors also developed papillary carcinoma later on in their lives. However, the same cannot be said for patients who received low-dose radiation exposure from imaging studies. Also, patients who did radiation therapy such as iodine-131 ablation of the thyroid did not develop papillary thyroid carcinoma presumably because cytotoxicity increases with these doses (38).

Aside from radiation exposure, papillary carcinoma has also been reported as a familial disease, occurring singly or in association with other familial syndromes. The RET proto-oncogene, a receptor protein tyrosine kinase encoded on chromosome 10, as a possible risk factor to late onset in life, prognosis is usually grim, with death occurring within months of confirmed diagnosis (40). Anaplastic thyroid carcinoma presents as a rapidly growing thyroid mass that is associated with local symptoms such as hoarseness and dyspnea in about half of the patients. Sometimes, patients will also present with vocal cord paralysis, and cervical metastases. Because of its rapid growth, at least one half of patients already have distant metastases (e.g. lungs, bones and brain) at the time of diagnosis. Gardner syndrome (familial adenomatous polyposis). Tumors typically appear late, about 10-20 years after exposure.

Papillary carcinoma is characterized by its slow-growth arising from T4 and thyroglobulin-producing follicular cells of the thyroid gland. These cells take up iodine, respond to TSH stimulation and synthesize thyroglobulin, all of which aid in the diagnosis and treatment of residual disease and recurrences after surgical excision. Tumors can pierce through the thyroid capsule to invade the trachea and other surrounding structures; invasion of the former results in hemoptysis and airway obstruction. Impingement of the laryngeal nerves causes hoarse, breathy voice and, sometimes, dysphagia. Involvement of the cervical lymph nodes is very common with the central compartment (level 6) being the most common site affected.

Hürthle cell carcinoma or oncocyctic carcinoma is a malignancy variant of follicular carcinoma, making up 2-3 percent of the overall thyroid cancer cases. It is characterized by Hürthle cells, which almost always makes up more than 75 percent of the tumor mass. Hürthle cells are large, polygonal follicular cells that contain abundant granular acidophilic cytoplasm. They are found in several benign thyroid conditions, such as Hashimoto thyroiditis, Graves disease, and multinodular goiter. Like other thyroid diseases, they are more common in elderly women.

Follicular carcinoma

Metastatic follicular carcinoma is the second most common form of thyroid cancer, accounting for about 10 percent of diagnosed cases. Populations who receive inadequate intake of dietary iodine have a high risk of developing follicular and anaplastic carcinomas (38).

The lesions produced by the rapidly growing follicles may stimulate the thyroid gland, resulting in high levels of thyroid hormones, or thyrotoxicosis. Excessive production of thyroid hormone happens rarely from functioning metastatic follicular carcinoma.

Medullary thyroid carcinomas (MTCs)

Medullary thyroid cancer (MTC) accounts for approximately 3-4 percent of all thyroid cancers. These tumors usually present as a palpable mass in the neck or thyroid, along with lymphadenopathy (39).

Approximately one-fourth of reported cases of MTC is familial. It is grouped into three syndromes (38):
- Multiple endocrine neoplasia syndrome IIA (MEN 2A)
- Multiple endocrine neoplasia syndrome IIB (MEN 2B)
- Familial non-MEN syndromes

MEN 2A is the most common of all three syndromes. Patients diagnosed with any of the above familial syndromes need to be screened for other associated endocrine tumors, particularly parathyroid hyperplasia and pheochromocytoma. Medullary thyroid cancer secretes calcitonin and other peptide substances, all of which are measured to track the progress of treatments received. Additionally, family members of diagnosed individuals should be screened for calcitonin elevation and/or for the RET proto-oncogene mutation to identify their risks for developing familial MTC (38). Aside from calcitonin, the cancer secretes corticotropin, serotonin, melanin, and prostaglandins.

Other reported cases of MTC are sporadic and occur unilaterally. Studies have pointed out the role of mutations in the RET (Rearranged during Transfection) proto-oncogene, a receptor protein tyrosine kinase encoded on chromosome 10, as a possible risk factor to developing medullary thyroid cancer. As a result, patients with this particular type of mutation can have the option to undergo prophylactic thyroidectomy.

Anaplastic carcinomas

Anaplastic or undifferentiated carcinoma is one of the rarest forms of thyroid carcinomas, accounting for only about 1.6 percent of all diagnosed cases. However, it is considered the most aggressive of all thyroid malignancies and offers one of the worst survival rates of all malignancies to stricken patients. They may be further grouped into small cell or large cell carcinomas. Like other thyroid diseases, it mostly affects women at a ratio of 3:1 for women. Patients with anaplastic thyroid carcinomas present much later compared to other thyroid malignancies, usually in the sixth or seventh decade of life. Because of its rapid progression, local invasive propensity and very late onset in life, prognosis is usually grim, with death occurring within months of confirmed diagnosis (40). Anaplastic thyroid carcinoma presents as a rapidly growing thyroid mass that is associated with local symptoms such as hoarseness and dyspnea in about half of the patients. Sometimes, patients will also present with vocal cord paralysis, and cervical metastases. Because of its rapid growth, at least one half of patients already have distant metastases (e.g. lungs, bones and brain) at the time of diagnosis. Primary thyroid lymphomas and primary thyroid sarcomas are rare.

EUTHYROID SICK SYNDROME

It refers to the abnormal findings on thyroid function tests that occur in patients with non-thyroidal illness (NTI), without present history of hypothalamic-pituitary and thyroid gland abnormalities. Recovery results in the full reversal of thyroid dysfunction (238).

Low T3 syndrome is a subcategory of this type of syndrome and characterized by several alterations in serum thyroid function test results in patients with different non-thyroidal illness without past or present history of thyroid or hypothalamic-pituitary disease. As the name suggests, decreased serum T3 and elevated rT3 are seen (238). Additionally, TSH, T4, fT4, and fT4 index (FTI) are variably affected depending on the severity and duration of the non-thyroidal illness. The more severe the illness gets, the lower the serum T3 and T4.
levels drops until gradually normalizing as the patient recovers. In its most severe form, there will be low T4 levels with elevation of TSH to hypothyroid levels at the recovery phase and finally returning to normal range levels at complete recovery. These thyroid function test alterations are most likely seen in the following illnesses (238):

- Gastrointestinal diseases
- Pulmonary diseases
- Cardiovascular diseases
- Renal diseases
- Infiltrative and metabolic disorders
- Inflammatory conditions

- Myocardial infarction
- Starvation
- Sepsis
- Burns
- Trauma
- Surgery
- Malignancy
- Bone marrow transplantation

It is worth noting that a lot of these patients with nonthyroidal illnesses also receive medications that affect thyroid hormone synthesis and metabolism.

### RISK FACTORS

The risk factors for certain forms of thyroid diseases have been partially discussed already. In the succeeding pages, more details will be discussed and explained.

#### Lifestyle risk factors

There are several lifestyle factors that contribute to the risk and development of thyroid diseases. These are:

- Smoking

#### Smoking

Smoking adversely affects the thyroid function, though studies have shown that this is not the case for all smokers. There are two suspected causative agents in cigarettes that interfere with thyroid function: nicotine and thiocyanate. Thiocyanate inhibits iodide transport potently. There are two proposed actions of thiocyanate on the thyroid gland. One is its prothyroid effects in euthyroid patients and second, is its anti-thyroid effects in patients with subclinical and evident hypothyroidism. In the case of the former, the existing circulating thyroid hormones may be enough to compensate for the noxious effects brought on by smoking. In the case of the latter, smoking leads to an elevated mean serum thyrotropin concentration and a higher ratio of serum T3 to free T4. Additionally, smoking has also been found to worsen the already slightly upset biochemical balance such as the serum lipid concentrations, putting patients at higher risk of developing cardiovascular events. It is also worth noting that subclinical hypothyroidism has also been identified as a strong indicator of risk for myocardial infarction. Finally, it has been found that smoking does not lower further serum concentrations of thyrotropin and thyroid hormones, rather, it aggravates the clinical signs and symptoms of overt hypothyroidism, upsetting further the delicate biochemical balance of the body (41).

Nonetheless, it seems more likely that the twin action of tobacco smoke is a result of the combined effects of the several components of smoke namely, nicotine, hydroxypropyridine metabolites and benzpyrenes, which may also interfere with thyroid function. It is not clear whether tobacco has any effect on the actions of thyroid hormone in the peripheries. Additionally, smoking may also indirectly influence thyroid function either through a long term and sustained sympathetic stimulation that results in increased secretion of thyroid hormones or by upsetting the delicate immunological balance.

Some studies strongly suggest smoking to be a risk factor for Graves hyperthyroidism, with severe Graves ophthalmopathy (GO) among those who smoke. Smoking induces immunogenic activity by altering the thyrotropin receptor, causing the retro-orbital tissues to be more susceptible to the antibodies. Another study showed stimulation of two other pathways upon which smoking is thought to act on and contribute to Graves ophthalmopathy (42):

- Stimulation of orbital fibroblasts increases glycosaminoglycans (GAG) levels, the soluble polysaccharides implicated in the pathology of eye disorders such as edema, extraocular muscle swelling, and proptosis.

- Stimulation of lipocyte differentiation and proliferation. This effect was synergistic with interleukin-1, and reversible by the administration of anti-interleukin-1 antibody. This may suggest that in order for cigarette smoking to induce Graves ophthalmopathy, the pre-existence of inflammatory reactions in the orbital tissues may need to be present. Furthermore, interleukin-1 might make a useful preventive agent against the development of Graves ophthalmopathy.

Moreover, smoking may also play a role in the dysfunctional restoration of tolerance to thyroid auto-antigens. Smoking is also associated with postpartum thyroiditis and antecedent of chronic autoimmune thyroiditis (41).

There are studies that link tobacco smoking to an increased prevalence of thyroid multinodular goiter, although not with solitary nodular goiter (41).

Alternatively, there are several studies that point to the protective effects of smoking from thyroid cancer. Results from a pooled analysis of 14 case–control studies gathered from the United States, Europe and Asia point to the link between cigarette smoking and reduced risk of thyroid cancer, particularly papillary and follicular cancers. The study further noted that the benefit was more pronounced in current smokers than former smokers, and illustrated the significant trends of reduced risk with longer duration and greater frequency of smoking. There are four proposed explanations for these findings (41):

- Firstly, the significant reduction of TSH secretion induced by smoking may play a role.
- Secondly, smokers have long been associated with lower body weight compared to nonsmokers, therefore, the risk for thyroid cancer may also be likewise lower.
- Thirdly, smoke possesses anti-estrogenic effects. This hypothesis is particularly significant since thyroid cancer has higher incidence among women, suggesting an etiology with estrogenic roots.
- Lastly, low levels of circulating thyroid autoantibodies correspond to lower incidence of hypothyroidism.

However, the role of these antibodies in the possible development of autoimmune hypothyroidism upon smoking cessation should also be considered. A study by Mestman et al. revealed a sharp but brief rise in the incidence of hypothyroidism in both men and women of all ages upon nicotine withdrawal. The researchers concluded that the incidence of clinical hypothyroidism is increased six times more within 2 years of quitting cigarettes. These findings point to the need
to consider hypothyroidism as the cause of untoward symptoms such as weight gain and tiredness in patients who recently stopped smoking (43).

Aside from thyroid hormones, it is also thought that smoking adversely affects adrenal cortical hormone levels by decreasing the enzyme activity of either 21- or 11-beta-hydroxylase in the adrenal cortex, resulting in greater release of male hormones in the adrenal gland. On the other hand, some studies have shown that the additive actions of nicotine to adrenocorticotropic hormone (ACTH) in the peripheries may lead to stimulation of adrenal steroidogenesis (41).

Aside from the steroid hormones, it is also thought that smoking contributes to elevated serum cortisol levels. Long term smoking is tied to elevated salivary cortisol, with stimulation of catecholamines release as a possible mechanism. This finding is backed by studies that found decreased serum cortisol levels in individuals who stopped smoking. The implication of the effects of smoking on cortisol levels is especially important when considering stress responses. There are two proposed mechanisms for the altered stress responses brought on by nicotine, namely (41):

- Decreased effects of nicotine on the affinity of receptors to catecholamine stimulation
- Chronic nicotine leads to reduced sensitivity to the stimulating effects of ACTH, prolactin, and growth hormone (GH).

**Stress**

The role of stress in the pathophysiology of Graves disease was put forward during the Boer War and World War I. Although, it is hard to pinpoint the exact effects of stressful events and the actual onset of Graves disease with retrospective analysis of studies, the role of stress on Graves disease is nevertheless recognized to be plausible. In the recent years, various clinical observations backed by modern advances in immunology and broader understanding of autoimmune diseases have proposed that stress hormones disrupt the balance of T-helper cell levels in the body (44).

Although Graves disease is thought to be a familial disease, heredity does not fully explain the pathophysiology of the disease. Environmental factors are thought to be responsible for 21 percent of the diagnosed cases. The table below lists these factors (46).

| Amiodarone | Iodine |
| Interferon-alpha (IFN-a) | Stress |
| CD52 | Tobacco |

Stress contributes to the risk of thyroid autoimmune disease by disrupting the tolerance mechanisms. The autoantibodies against the TSH are specifically T-helper (Th) cell dependent. Graves’ disease was predominantly considered to be the result of Th2 expression but recent studies have found that the disease could also be mediated by Th1 antibodies as well. Indeed, the same TSHR can trigger the differentiation of Th1 or Th2 cell types. Another type of inflammatory cells that has been implicated in thyroid autoimmunity disease, the Th17 cells which generate interleukin 17 (IL17). Its pathophysiological role has been demonstrated clearly in IL17-deficient mice model. Th17 cells on the other hand have been associated with Hashimoto’s thyroiditis. In another note, the complexity of the Th1/Th2/Th17 mediation has also been demonstrated in the thyroiditis mice model, with both Th1 and Th2 cells showing vital roles for the development of the iodine-induced autoimmune thyroiditis in non-obese diabetic mice (47).

A study published recently found a strong link between the degree of stress, intensity of symptoms and the biological status with the first onset of Graves disease. Participants belonging to the older age group were found to exhibit hyperthyroidism of lesser severity and lower fT3 and fT4 serum levels, revealing the clinical effects of stress on Graves disease. Another study on patients treated with radioactive iodine found the potentiating effects of stress on autoimmunity. The results showed that patients with history of stress were later on more affected by hypothyroidism. Additionally, two other studies implicated the role of stress in the delayed improvement of thyroid disease following antithyroid drug therapy (48).

The stress system is composed of the corticotropin-releasing hormone (CRH) and locus ceruleus-norepinephrine (LC/NE)-autonomic centers in the brain stem, the hypothalamus, and mesolimbic dopaminergic pathway. The system directs the coping mechanisms of the body to stressors to improve survival. When activated, these components bring about a variety of responses, namely (45);
only on Th1 cells. Their agonists suppress the production of IFN-γ by Th1 cells. Moreover, the stimulation of epinephrine–lipopolysaccharide dendritic cells secretes IL12 and IL23 for IL4 and IL17 production by effector T-cells. The resulting Th2/Th17 setting is linked to many autoimmune diseases (50).

Glucocorticoid and catecholamine mediated actions on the immune system are not the only pathways that are associated with autoimmune diseases. Depression and stress stimulate the release of inflammatory cytokines, such as interleukin-6, dendritic cells and macrophage-produced cytokine. The increased interleukin-6 levels during stress causes a disruption in the Th1/Th17/Treg balance. Additionally, NF-κB is also produced after stress, which in turn stimulates NF-κB signaling in mononuclear cells. The role of cytokines in regulation mechanisms can trigger Treg stimulation and release, affecting the development of Graves disease (51).

Pregnancy

There are two hormones that are elevated during pregnancy—human chorionic gonadotropin (hCG) and estrogen—which increases serum thyroid hormone levels. As mentioned above, hCG is secreted by the developing placenta and is structurally related to TSH, able to stimulate the thyroid to produce excess thyroid hormones. The elevated presence of estrogen in turn results in the increased amount of thyroxine-binding globulin in the body, making thyroid hormone transportation in the blood easier and faster. Additionally, the thyroid gland slightly increases in size in healthy women during pregnancy, but not noticeable enough to be detected during a routine physical check up, a condition called subclinical hyperthyroidism. On the other hand, if the gland is enlarged enough to be detected, a strong sign of thyroid disease, it should be assessed as soon as possible. The hormone level alterations, increased thyroid size and other symptoms common to both pregnancy and thyroid disease make the latter’s diagnosis difficult (52).

Hyperthyroidism in pregnancy

The incidence of hyperthyroidism in pregnancy is largely attributed to Graves disease, occurring in a ratio of 1:500 pregnancies (52). Although Graves disease may make its initial appearance during pregnancy, a woman who is already diagnosed with it may actually experience symptomatic improvement during the second and third trimesters. The remission may be a result of the overall immune system suppression occurring during pregnancy. However, the disease exacerbates during the first months following delivery. Graves disease during pregnancy should be monitored monthly (53).

Another condition during pregnancy that can possibly precipitate hyperthyroidism is hyperemesis gravidarum, an extreme case of nausea and vomiting that often results in weight loss and dehydration. The elevated levels of hCG is thought to be the triggering factor to the condition as well as the transient hyperthyroidism during the first trimester.

Uncontrolled hyperthyroidism during pregnancy can affect the baby in a number of ways, namely;
- It can cause congestive heart failure
- It can cause preeclampsia
- It can cause thyroid storm
- It can lead to miscarriage
- It can lead to early labor
- It can lead to low birth weight

It is worth noting that women who underwent radioactive iodine therapy or surgery to correct Graves disease in the past may still have existing TSI antibodies in the blood even when thyroid levels have reached normal levels. These antibodies cross the placental barrier into the fetal bloodstream, stimulating the thyroid gland. However, if the mother is under anti-thyroid medications, the fetus may not develop hyperthyroidism because these drugs also cross the placental barrier and enter the fetal circulation.

Untreated hyperthyroidism in infants may result in tachycardia, which in turn may lead to heart failure, congenital malformations, poor weight gain, irritability, and rarely, an enlarged thyroid that protrudes into the trachea, obstructing the airway and interfering with breathing.

Hypothyroidism in pregnancy

Generally, the hypothyroidism that occurs during pregnancy can be mainly attributed to the autoimmune disorder, Hashimoto’s thyroiditis. Untreated, or undertreated, hypothyroidism may very well lead to serious fetal and maternal risks such as pre-eclampsia, placental abnormalities, low birth weight infants, and postpartum hemorrhage. Like subclinical hyperthyroidism, mild hypothyroidism is also hard to detect because of the similarity of its symptoms with pregnancy (53).

Postpartum thyroiditis (PPT) occurs in 4-10 percent of women. It is a variant of the chronic Hashimoto’s thyroiditis and its causes are also rooted in autoimmune mechanisms that usually develop during the first year following delivery. Its peak incidence is at 6 months. It is characterized by the presence of antimicrosomal antibodies and manifests clinically as transient thyrotoxicosis, hypothyroidism, or transient thyrotoxicosis followed by hypothyroidism. Although the manifestations may not always be unrecognizable, their early detection is important in preventing exacerbation into permanent hypothyroidism (53).

PPT proceeds in three stages:
1. Hyperthyroid stage: T3 and T4 release due to thyroid destruction
2. Hypothyroid stage: Lower T3 and T4 levels due to the destroyed gland
3. Euthyroid stage: Resolution of thyroiditis

They occur within a year after delivery and detecting it is crucial since some women may get pregnant right away. Symptoms vary depending on the stage of the disease at the time of symptomatic manifestation and diagnosis. Women who had or have current autoimmune thyroid disease should get their thyroid antibody values assessed at the end of the first pregnancy. Women who tested positive for thyroid receptor-stimulating antibodies or are taking anti-thyroid medications should undergo fetal ultrasound at least once a month after twenty weeks of gestation (53).
Conception and hypothyroidism

Women with diagnosed hypothyroidism need to have their medications dose adjusted prior to trying to conceive, with a TSH goal of <2.5 percent. Additionally, women need to have their thyroid medication dose increased by 25-30 percent as soon as pregnancy is confirmed (53).

Fetal thyroid dysfunction presents with a heart rate of more than 160 beats per minute, fetal goiter, hydrops and intrauterine growth restriction.

The risk and severity of fetal or infantile hypothyroidism is related to the mother’s level of thyroid receptor antibodies due to transplacental transfer. As such, fetal or infantile hypothyroidism may also be due to maternal intake of anti-thyroid medications.

Generally, fetal and maternal health outcomes vastly improve with rapid resolution of thyroid dysfunction.

Aside from the risk factors discussed above, there are other contributing causes to thyroid diseases.

AGE

Thyroid cancer

The incidence of thyroid cancer can occur at any age, though its risk increases earlier for women when compared to men. Women are usually diagnosed during midlife while men who are diagnosed are usually already well in their 60s or 70s (54).

Hyperthyroidism

Like other hyperthyroid patients, bodily processes such as metabolism tend to speed up. However, while the younger patient may often exhibit multiple symptoms of the disease, an elderly patient may only have one or two of those, making diagnosis difficult in this population group (55).

Hypothyroidism

An increased prevalence of hypothyroidism has been consistently found in the elderly population. Although there are several factors that are thought to contribute to the widespread prevalence, almost all studies report higher rates for both overt and subclinical hypothyroidism in women with advancing age.

Furthermore, the incidence ratio of undiagnosed hypothyroidism in nursing home residents over 60 years old is approximately 1:4. The risk increases with age (56).

Unlike symptoms of hyperthyroidism, clinical manifestations of hypothyroidism are very broad to be classified under one distinct subset of symptoms and this is even more so in the case of elderly patients. For example, memory loss and decline of cognitive function is often associated with the natural processes of aging but at the same time, these two may be the only presenting symptoms of hypothyroidism. Other symptoms such as weight gain, sleepiness, dry skin, and constipation, may also be present but lack of these symptoms does not rule out the diagnosis. In order to make a confirmed diagnosis, clinicians often need a high index of suspicion such as a positive family history of thyroid disease and extensive history of radiation therapy around the neck area (56).

Gender

Thyroid diseases are more common among women. Several epidemiological studies in adult population strongly suggest a greater prevalence of thyroid disease in the female gender.

The sex-related differences in the prevalence of hyperthyroidism is not clearly defined although a lot of the diagnosed cases of Graves disease and toxic multinodular goiter proportionally increase or decrease with dietary iodine intake. Another factor to consider is the underlying nodularity and functional autonomy of the thyroid gland which may become more overt as iodine exposure increases (55).

Like other forms of hyperthyroidism, subclinical hyperthyroidism is more common among women than men, especially in patients more than 70 years of age. Declining T3 levels is common in the elderly and because low T3 is often a result of other underlying diseases, it is difficult to clearly identify a sex-related difference in its prevalence.

On the other hand, an independent association of low-T3 levels with men has been found in elderly patients living at home.

Advancing age is an important contributing factor to assessing the aggressiveness of thyroid cancers. Both follicular and anaplastic variant of thyroid cancer are more prevalent in the elderly.

Epidemiological studies on the aging population reiterate the fact that men are less affected by thyroid disease than women. However, elderly males may still be at risk for thyroid cancer, a point to remember in the evaluation of thyroid nodules among the geriatric population (55).

In another note, a study by Hsieh et al. showed that men diagnosed with papillary thyroid cancer and underwent thyroidectomy had poorer prognosis. Specifically, males exhibited higher thyroid cancer mortality rates than females. Multiple regression analysis pointed to the male gender being an independent risk factor for thyroid cancer recurrence and death (58).

Nitrate intake

A study by Ward et al. in 2010 found an association between nitrate contamination and risk for thyroid disease. Nitrate contamination of food and drinking water is a potential source of nitrate intoxication that can lead to thyroid dysfunction. Once ingested, nitrates are converted into nitrates, chemical substances that compete with iodide uptake by the thyroid, reducing the available iodine needed for normal thyroid hormone production (57).

Specifically, the study found an increased risk of thyroid cancer with nitrate levels in the public water supply exceeding 5 mg/L. However, there was no distinct link with the prevalence of hypothyroidism or hyperthyroidism. Dietary nitrates also exhibited similar effects on thyroid function. The hypothesis that nitrate-contaminated water plays a role in the etiology of thyroid cancer warrants further study (57).
Juvenile diabetes

According to a study by Betul et al. of Cleveland, Ohio, individuals with juvenile diabetes are more likely than others to develop autoimmune thyroid disorders. It also reiterated the fact that women are about 8 times more likely to develop thyroid disease (59).

Thyroid diseases and juvenile diabetes are “sister diseases”, in the sense that they have the same root cause – autoimmunity. The antibodies for each disease are different. Additionally, having an autoimmune disease puts the individual at risk of another autoimmune disease. These diseases also have familial roots; an example is a grandparent with hyperthyroidism and an offspring with juvenile diabetes.

The most common thyroid disorder associated with juvenile diabetes is Hashimoto’s thyroiditis while 10 percent of diagnosed cases developed Graves disease. Generally, juvenile diabetes occurs first and followed by thyroid dysfunctions at some point in the future. However, this isn’t always the case. Many people are first diagnosed with juvenile diabetes during midlife, making way for the possibility of the reverse order of occurrence. Moreover, untreated thyroid conditions adversely affect blood sugar levels in individuals with juvenile diabetes. Also, the unexplained weight gain associated with insulin use may be attributed to an undertakable thyroid (59).

In the beginning, autoimmune thyroid disease can present as episodes of hypothyroidism followed by normal thyroid levels. The symptomatic episodes can happen on and off as the thyroid is being continuously damaged by the immune system (59).

Obesity

Central obesity is associated with many endocrine disorders including thyroid dysfunctions. T3 regulates glucose and lipid metabolism and thermogenesis. Thyroid dysfunction is independently linked to body weight and composition alterations, body temperature shift, and total and resting energy outflow. Sometimes, the onset of weight gain occurs after thyroid dysfunction treatment. Results from past studies propose slight variations in thyroid function such as those in subclinical thyroid diseases to be risk factors to the development of regional obesity and weight gain risk (60).

Furthermore, body mass index has been adversely associated with T4, fat accumulation with decreased T4 (61) (62) and elevated TSH levels with overweight but euthyroid individuals, pointing to a positive correlation between TSH and the inevitable weight gain over time (63).

Adipose tissues are part of the endocrine system because they produce and release leptin (64). The relationship between TSH and body mass index may be due to the leptin produced by fat tissues. Leptin inversely affects thyroid hormone production and release, and endocrine activity in many ways. Firstly, it plays an important physiological role in regulating energy homeostasis (65). It works in conjunction with the central nervous system in altering neuroendocrine and behavioral responses to overeating, maintaining a balance between energy intake and expenditure. Secondly, leptin also regulates the hypothalamic-pituitary-thyroid (HPT) axis (65) (66) through TRH gene expression in the paraventricular nucleus, an action that results in TSH-stimulated leptin release by the adipose tissues (66) (67) (68).

Lastly, it affects thyroid deiodinase activities with activation of the T4 to T3 conversion (64) (69). A good example is the altered thyroid function occurring with normal feedback regulation in subclinical hypothyroidism. It may be the critical event that stimulates energy expenditure changes with resulting BMI and weight elevations.

Diet

Unhealthy diet with deficient nutrients plays an important role in the development of various thyroid disorders. These nutrient deficiencies are listed below and discussed in detail in the succeeding pages (70):

- Vitamin B12
- Selenium
- Vitamin D
- Iodine

Iodine

Iodine deficiency has been cited as the most common cause of thyroid disorder in developing countries, which ultimately leads to goiter formation and hypothyroidism (71).

Iodine deficiency has been reported to be the major risk factor for the growth and development of hypothyroidism in approximately 800 million people inhabiting the iodine deficient areas of the world (72).

Iodine is an essential requirement that functions as the substrate for the synthesis of thyroid hormones. The minimum daily requirement of iodine is approximately 50 micrograms. Both deficiency and excess of iodine creates an imbalance in the thyroid hormonal regulation. When the supply of iodine changes (e.g., excess iodine intake), an auto-regulatory mechanism is activated to prevent further changes. This mechanism is also referred to as Wolff–Chaikoff effect and escape (73).

As mentioned previously, iodine deficiency is the most important risk factor for goiter and it has been shown in studies that “characterization of iodine status of a population has a central role in thyroid epidemiology” (74). It has also been suggested that the knowledge of iodine intake level of a certain geographical area or a particular population is very important in understanding the pattern and prevalence of thyroid disorders and planning for their medical surveillance and treatment (75).

Research has shown that even small fluctuations in iodine intake level have an impact on the prevalence of goiter, nodules, and thyroid dysfunction. A relative decrease in the serum concentration of thyroid stimulating hormone occurs with age in the case of mild to moderate iodine deficiency.

Iodine deficiency

Iodine deficiency has severe pathologic consequences including endemic goiter, endemic cretinism, increased fetal and infant mortality and enhanced prevalence of motor and neuromotor disabilities in large populations (73). It has been reported that the overall health status of a population is affected by developmental brain disorders and goiter resulting from iodine deficiency and this in turn, adversely affects the overall performance and financial status of a population. The onset and prominence of the thyroid abnormality are directly related to the low intake of iodine. Severe iodine deficiency needs immediate attention while less severe iodine deficiency results in multinodular autonomous growth and function of the thyroid gland which eventually leads to goiter and hyperthyroidism among the middle aged and elderly individuals (76).

Iodide oxidation to iodine is essential in thyroid hormogenesis. A deficiency of iodine may result in oxidative stress, high concentration of thyroid stimulating hormone (TSH) and increased concentration of hydrogen peroxide which cannot be used in the synthesis of thyroid hormones since the iodide molecule is lacking (77).
Excess iodine

Excess iodine ingestion commonly results from the use of medicinal preparations of iodine or radiographic contrast media. It can especially lead to serious pathologic consequences in cases where thyroid auto-regulation is defective or absent such as fetal and neonatal thyroid Hashimoto's thyroiditis. Multinodular goiter may result from defective thyroid auto-regulation mechanism and an excess of iodine in this situation can result in thyrotoxicosis or Jod-Basedow disease (73).

Many studies have shown that severely excessive intake of iodine is associated with a hypofunctional thyroid and goiter in children. A moderate to mild excess of iodine are associated with hypothryoidism, with elderly individuals being the most likely affected (76). Additionally, excess iodine exerts a cytotoxic effect on the thyroid cells as a result of formation of free radicals. Necrotic and apoptotic mechanisms with necrosis are believed to be at play in the development of goiter and apoptosis during iodide-induced thyroid involution (77).

It has been reported that the pathologic manifestation of iodine excess can be readily eliminated when the source of iodine is removed (73).

Goitrogenic foods

Goitrogenic foods are naturally occurring substances which interfere with the normal functioning of the thyroid gland. Such substances have the ability to enhance the size of the thyroid to compensate in cases where there is low production of thyroid hormones.

Foods containing goitrogens are classified in two classes:

- Soy and soybean related foods
- Cruciferous vegetables

Research has reported an increased risk for thyroid dysfunction in parts of Central Africa where consumption of cassava root and cassava flour is prevalent. Excessive intake of isothiocyanates along with a deficiency of dietary selenium can lead to thyroid disorders.

Soy and soy-related goitrogenic foods

Soy-related foods such as tofu and tempeh contain isoflavones that are associated with reduced thyroid hormone output. Most of the research has demonstrated that flavonoids have many health benefits but there is also current mounting evidence that suggest its role in reduction of thyroid function. Moreover, the presence of isoflavones like genistein inhibits the activity of the enzyme thyroid peroxidase (91).

Among the many foods which are considered as risk factors for developing thyroid diseases, soy and soy-related foods ranks high as one the most frequently cited. Studies have reported that the soy intake can induce or lead to hypothyroidism. Additionally, soy-related foods interact with the absorption of drugs used in the treatment of thyroid disorders (78).

Soy foods may also accelerate the underlying autoimmune process that is responsible for Graves disease and Hashimoto’s thyroiditis. A randomized, double blind, cross over study where none of the subjects had prior thyroid surgery or radioiodine therapy, showed that increased soy food intake corresponded with a relatively higher risk of TPO-negative autoimmune subclinical hypothyroidism to overt hypothyroidism by three times (80). This finding suggests keeping a close eye and monitoring vegetarians who use soy a lot in their diet.

The effect of soy isoflavones on thyroid disorders

The active constituents present in soy foods are estrogenic isoflavones, with genistein, daidzen, malonylgenistin and malonyldaidzin among the most common (81). Studies have shown that soy isoflavones interfere with the activity of the enzyme thyroid peroxidase, which is the primary enzyme involved in the synthesis of T3 and T4, thus, interfering with their subsequent formation (79). Furthermore, the isoflavones found in soy also prevent the uptake of iodine into the thyroid cells by interfering with the mechanism of the sodium-iodide symporter (82). The phytoestrogens present in soy foods are known to interfere with the absorption of thyroid hormone from the stomach. This effect may further worsen the thyroid function especially in those cases where there is preexisting mild hypothyroidism (80).

Soy foods may also accelerate the underlying autoimmune process that is responsible for Graves disease and Hashimoto’s thyroiditis. A randomized, double blind, cross over study where none of the subjects had prior thyroid surgery or radioiodine therapy, showed that increased soy food intake corresponded with a relatively higher risk of TPO-negative autoimmune subclinical hypothyroidism. There is no sufficient data reporting the effect of long term exposure to soy foods on thyroid function, although gastrointestinal side effects have been reported (80).

Interrelationship between iodine and soy consumption

It has also been found through various studies that the presence of iodine deficiency markedly increases the anti-thyroid effects of soy foods. Other factors such as defective hormone synthesis and other goitrogenic dietary sources can also cause overt thyroid toxicity (83). Soy food and supplements, in excessive quantities, are contraindicated in individuals with diagnosed autoimmune thyroid disease or goiter (80). Research studies have reported that consumption of excessive isoflavones found in soy in combination with iodine deficiency reduced thyroid function in both animals and in humans.

Research reports have enumerated three other factors which are associated with an increased risk for thyroid dysfunction when present in combination with high intake of soy foods. These are (84):

- Colitis, poor gastrointestinal absorption or other disorders associated with the intestine.
- Metabolic problems of the liver
- Stimulation of thyroid enzymes, receptors or hormones for antibody production by the immune system.

There is no definitive evidence that an increased dietary intake of soy foods (such as tofu, tempeh, natto, soy miso and soy sauce)
daily can increase the risk of thyroid disorders in the presence or absence of iodine deficiency or the other factors. However, it is highly recommended that people with iodine deficiency, intestinal, liver or immune system disorders to consult their clinicians before taking soy supplements or increasing their daily intake of soy foods. Moreover, the adverse effects on the thyroid gland are more pronounced if consumption of goitrogenic foods is compounded by selenium deficiency, iodine deficiency or liver, intestinal or immune system disorders.

**Soy in infant foods**

Research studies on animal subjects have reported an increased risk and frequency of autoimmune thyroid disorders in infants. The isoflavones present in soy infant formulas have raised concerns regarding their adverse effect on the various organs including the thyroid gland. It has also been reported that the management of congenital hypothyroidism becomes very complicated if infants also consume soy based formula. Some studies have suggested close monitoring of infants being treated with higher doses of levothyroxine for hypothyroidism. However, there is a lack of sufficient evidence regarding the effect of soy-containing formulas on euthyroid infants or those with iodine deficiency (85).

Additionally, research studies have shown that soy containing infant formulas increase the probability of autoimmune thyroid diseases in infants who are fed exclusively on these formulas. Infants who are predisposed to thyroid problems before the consumption of soy based infant formula are more prone to acquiring thyroid dysfunctions.

**Cruciferous vegetables**

Cruciferous vegetables such as broccoli, brussels sprouts, cabbage, cauliflower, kale, kohlrabi, mustard, rutabaga and turnips contain isothiocyanates. Isothiocyanates, like isoflavones, are associated with a reduction in thyroid function. Isothiocyanates also inhibit the enzyme thyroid peroxidase and block neural messages across cellular membranes of thyroid cells (86). Research into the role of cruciferous vegetables in thyroid function points to the fact that increased intake of the latter alone cannot cause thyroid disorders. However, those with existing or past history of thyroid disorders must consult their clinician before consuming large and regular quantity of raw cruciferous vegetables such as broccoli.

**Nuts**

The goitrogens in nuts inhibit the uptake of iodine and block the binding of iodine to tyrosine, thus, inhibiting the synthesis of thyroid hormones (88).

**Effect of heat on goitrogenic foods**

It has also been noted in limited research studies that cooking may inactivate the goitrogenic components of foods. Isoflavones and isothiocyanates are heat labile and their biological effects are reduced with heating. For instance, boiling broccolis in water reduces their isoflavone content by almost one third of the original.

**History**

A personal history of any autoimmune disease slightly increases the risk of developing an autoimmune thyroid disease such as Hashimoto’s disease or Graves disease. Autoimmune thyroid disorders are classic examples of organ specific autoimmune disorders. There are many factors, both genetic and environmental which give rise to autoimmune disorders such as the involvement of the genes lying in the HLA complex and CTLA-4, smoking, stress and excessive iodine intake (92). Thyroid disorders such as hypothyroidism are associated with raised levels of serum TSH alone while the presence of thyroid antibodies increases the probability of developing autoimmune diseases (93).

**Genetic factors of autoimmune disorders**

Autoimmune thyroid diseases (including Graves disease and Hashimoto’s disease) result from a complex interaction of environmental factors and genetic factors. Epidemiological, family and twin studies have proven that there is a strong genetic influence on the development of autoimmune thyroid disease (94). The MHC class II (Murine major histocompatibility complex) alleles have been found to be associated with Graves disease. The presence of the antigen, HLA-DR3, is another risk factor for these autoimmune diseases. CTLA-4 is also an immunomodulatory molecule present in T cells which plays a key role in the autoimmunity in Grave’s disease (95).

Graves disease and Hashimoto’s thyroiditis are reported to be genetically distinct. Patients with Graves disease being treated with anti-thyroid drugs have shown familial clustering and a late occurrence of spontaneous hypothyroidism. The only common pathogenesis between Grave’s disease and Hashimoto’s thyroiditis is the genetic involvement of CTLA-4 (92).

Autoimmune diseases progress in thyroid cells through interactions with the immune system and release of various immunologically active molecules (HLA class I and II, adhesion molecules, cytokines, CD40 and complement regulatory proteins). Thyroid autoantibodies and focal thyroiditis occur with greater frequency (96). Graves disease and Hashimoto’s disorders are closely related autoimmune diseases which are known to cause thyroiditis (97).

**Graves disease**

It is an autoimmune disorder which ultimately progresses to overactivity of the thyroid gland, or hyperthyroidism. Graves disease, a hyperthyroid condition with diffuse goiter, is the most common cause of thyroid disease in the US (100). An abnormal immune response induces the release of excess T4 and T3 into the blood, thus, causing hyperthyroidism (98). Hyperthyroidism has also been mentioned as one of the symptoms of Graves disease (99).
Hashimoto’s disease

Chronic autoimmune thyroiditis has been classified in two forms;
- Goiterous form (often referred to as Hashimoto’s disease)
- Atrophic thyroiditis

The correlation between autoimmunity and autoimmune thyroid disorders

Autoantigens produced and found in patients with autoimmune thyroid disorder are recognized to exhibit intra and inter-individual heterogeneity. The cytokines produced indicate the involvement of both the Th1 and Th2 limbs of the helper T cell response. The secretion of chemokines and cytokines in the thyroid helps in the accumulation and expansion of the intra-thyroidal lymphocyte pool.

Thyroid cells themselves are involved in this secretion. Along with chemokines and cytokines, thyroid cells also produce a number of proinflammatory molecules which enhances the autoimmune response. T cell mediated toxicity is responsible for the destruction of the thyroid cells in autoimmune hypothyroidism. It also mimics the effect of death receptor mediated apoptosis.

Drugs

There are drugs used in the treatment of different non-thyroidal conditions that are known to adversely affect the thyroid function. Often these effects on the thyroid function are their side effects. As discussed previously, these drugs are amiodarone, interferon, lithium, kelp tablets and dietary supplements. Patients taking these drugs should be monitored routinely for the presence of any thyroid disorders. The use of iodide containing medicines can induce hyperthyroidism within 3-8 weeks of administration. Iodides are known to cause hypothyroidism but they may also induce goiter and hyperthyroidism.

According to research studies, the incidence of amiodarone-induced thyroid disease is approximately 2 to 24 percent of the population. The prevalence of hyperthyroidism has been reported in 1 to 5 percent of the patients. There are two types of hyperthyroidism induced by amiodarone, namely; Type 1 Graves disease and Type 2 subacute thyroiditis resulting from the direct toxic effect on the gland.

Likewise, there have been reports of patients taking lithium carbonate diagnosed with lithium-induced hypothyroidism and subclinical hypothyroidism. A research study has reported a prevalence rate of 5 to 20 percent of patients, while other studies reported almost as high as 50 percent of patients. The drug is also known to induce non-tender goiter. Lithium is known to accumulate in the thyroid gland and adversely affect the synthesis and release of thyroid hormones. The period of exposure to lithium treatment is reported to be directly proportional to the risk of developing hypothyroidism.

Interferon-alpha used in the treatments of tumors and Hepatitis C has been known to cause autoimmune destruction of thyroid cells, leading to a modified level of thyroid hormones in the blood stream. However, when interferon beta-1b is used in treatment of multiple sclerosis, it is not known to induce thyroid dysfunction. The thyroid disorder that developed during interferon therapy is transient in nature according to research reports.

Research studies have reported that women are more affected by drug-induced thyroid disorders when compared with men. People who have thyroid antibodies before the start of therapy are also at an increased risk of getting induced thyroid disorders.

Tyrosine kinase inhibitors are a class of drugs which are used in the treatment of neoplasms such as thyroid cancer. Research has reported that they can cause thyroidal side effects. They can adversely affect thyroid hormone metabolism and affect patients who are being given thyroid replacement therapy.

Similarly immune modulators are also known to cause hyperthyroidism and hypothyroidism. Lithium has also been known to bring about anti-thyroid effects; affect the absorption, metabolism and transport of thyroid hormones. Research studies have shown that lithium activates the production of antibodies against thyroid cells and causes hypothyroidism.

Salicylates like aspirin, salicylic acid, methyl salicylate, sodium salicylate and diflunisal are known to affect the concentration of thyroxine in the blood. They displace thyroxine from the thyroxine-binding globulins and induce thyroid disorders. Topical products containing salicylates used to treat acne and skin disorders have not been reported to induce any thyroid disorder.

There are also medications which affects the metabolism of T4. Drugs like rifampin, rifabutin, phenytoin, carbamazepine and phenobarbital are known to enhance the metabolic removal of T4 and T3 which creates complications in patients who require thyroxine replacement therapy. Similarly, the use of ritonavir increases the glucuronidation of thyroxine, thus necessitating an increase in the dose of thyroxine. The use of serotonin reuptake inhibitors (SSRIs) is also associated with modifications in the requirements of T4. Other drugs adversely affect the absorption of exogenous thyroxine. Drugs such as iron, aluminum-containing products (e.g. sucralfate, antacids, and didanosine), sodium polystyrene sulfonate, resin binders and calcium carbonate have been reported to inhibit the absorption of exogenous thyroxine and reduce their efficacy as well.

Treatments affecting thyroid function

Radiotherapy (used as treatment for head and neck tumors) cause damage to the thyroid cells and cause hypothyroidism to occur. Patients with chronic kidney disorder undergoing hemodialysis are reported to have very low concentration of thyroid hormones and increased concentration of TSH in their blood. Uremic patients have shown a minor increase in the subclinical levels of TSH. The use of heparin is also associated with inhibition of the binding of T4 to proteins, thus releasing a fraction of T4 in patients with chronic kidney disease following heparin dialysis. Patients undergoing peritoneal dialysis are reported to experience more pronounced symptoms of subclinical hypothyroidism accompanied by low levels of T3. Additionally, it has been seen that the reduced concentration of T3 and T4 are transient and recover to normal levels once the cause of chronic kidney disease related abnormalities have been corrected.

Research has reported that the occurrence of thyroid carcinoma is one of the most commonly prevalent malignancies in patients who underwent kidney transplant. Moreover, studies have also found that therapy with T3 supplement is not necessary for survival of the patients who have undergone transplantation.
The signs and symptoms of thyroid disease are often general and nonspecific. Each subset of thyroid disease is discussed in detail, with special emphasis on the neurological manifestations in the elderly populations.

**Subclinical thyroid disease**

In 2002, a group of experts from the American Thyroid Association (ATA), the American Association of Clinical Endocrinologists (AACE), and the Endocrine Society (ES) convened and defined the meaning of “subclinical thyroid disease”. The committee has defined it as “a serum TSH concentration above the statistically defined upper limit of the reference range when serum fT4 concentration is within its reference range”. The committee of experts has also set the reference range for serum TSH to be 0.45 to 4.50 μU per mL (108).

Additionally, the committee weighed in the risk vs. benefit ratio of current treatment guidelines and made recommendations and guidelines on the assessment and monitoring of the adult population (108). These recommendations and guidelines are discussed further under the section, “Preventive and Screening Measures”.

**Subclinical state**

The subclinical thyroid disorders are the preclinical stage of the actual diseases; they don’t represent the disease itself. They are considered strong predictors for thyroid disease. In fact, they are actually laboratory evident diagnosis with no symptoms. The patient may remain completely asymptomatic or may feel mild degrees of thyroid dysfunction at this stage.

The subclinical thyroid disorders are classified into subclinical hypothyroidism and subclinical hyperthyroidism. Both are laboratory diagnoses with nonspecific symptoms; TSH levels below 0.45 μU per mL and above 4.50 μU per mL are considered hyperthyroid and hypothyroid states, respectively. If left untreated, both can lead to serious thyroid dysfunction. It is therefore crucial for the clinician to weigh in the risks and benefits of each patient individually; i.e. will a potential initial treatment do more harm than good or vice versa. (110)(111).

Each subclinical state will be discussed individually in the succeeding pages.

**Subclinical hypothyroidism**

In subclinical hypothyroidism, the serum TSH level of the patient remains slightly elevated without affecting the serum fT3 and fT4 levels, which remains within the normal range throughout this stage.

As mentioned above, patients usually exhibit nonspecific symptoms. These are outlined in detail below (109):

1. General: Fatigue even during routine work, lower energy levels as compared to others, increased sensitivity to cold temperature, unexplained mood swings, and unexplained weight gain.
2. Skin and hair: Altered skin appearance. The skin becomes dry and flaky. It may become pale or yellowish in appearance. Hairs also become dry, with apparent moisture loss and become brittle.
3. Psychological: Thyroid hormone imbalance has extensive effects on the brain. Symptoms include constant exhaustion, mood swings, depression, irritability, unexplained angry reactions, and loss of interest in the surroundings and day to day work.
4. Gastrointestinal: Increased level of TSH level affects bowel movement producing symptoms such as constipation, indigestion and loss of appetite.
5. Ear, nose and throat: Occasional swelling of the thyroid gland affects the speech of the patient which leads to voice hoarseness and occasional hearing difficulties.
6. Female reproductive organ: Hormonal imbalance leads to disturbance in the menstrual cycle, exhibiting as menorrhagia and irregular menstruation.
7. Cardiovascular: Thyroid dysfunction may also manifest as bradycardia.
8. Musculoskeletal: Patient may exhibit symptoms such as muscle pain, fatigue, frequent and painful muscle cramps, and stiffness of the joints. Neck stiffness and back pain are invariably present in many of the female patients.
9. Laboratory findings: The findings usually show slight elevations of serum TSH while serum Ft3 and F4 remain within the normal range. Additionally, some patients may show slight abnormalities with their lipid profiles. They may have mildly elevated triglyceride and LDL levels.

**Subclinical hyperthyroidism**

Subclinical hyperthyroidism manifests with low or undetected serum TSH level in the patient with normal T3 and T4 levels. Its symptoms are discussed in detail below (109):

1. General: Symptoms such as persistent fatigue, tremor, malaise and reduced feeling of well being are very common. The patient may also experience increased propensity to sweat and greater intolerance to heat. The significant symptom is unexplained weight loss.
2. Gastrointestinal: The patient may have frequent bowel movements and increased appetite.
3. Psychological: The patient may experience random mood swings and fluctuating energy levels characterized by hyperactivity immediately followed by fatigue. Constant nervousness, anxiety, fear, hostility and sleep disturbances are seen in subclinical hyperthyroidism. Additionally, the patient may have difficulties concentrating.
4. Skin and hair: Sweat glands become overactive and lead to hyperhidrosis and hair loss.
5. Cardiovascular: Patient may experience palpitations. Since thyroid level affects the neurohormonal regulation of the cardiac function, the patient may become tachycardic and carry a higher risk of developing supraventricular arrhythmias. 2D echo often gives an evidence of left ventricular hypertrophy and impaired diastolic function.
6. Female reproductive organ: Decreased thyroid level may lead to menstrual abnormality and even amenorrhea.
7. Musculoskeletal: The patient may have reduced bone mineral density (BMD) accompanied by accelerated osteoporosis and thinning of bones, making the patient susceptible to bone fractures. This symptom is very common in post-menopausal women. Additionally, the patient often complains of vague muscular pain and muscle weakness.
8. Neurological: Tremors, vertigo are some of the neurological symptoms of subclinical hyperthyroidism. Since it usually occurs in elderly women, it may be confused with age-related dementia and Alzheimer’s disease.
9. Laboratory findings: The blood tests will show low or undetectable levels of TSH with T3 and T4 levels remaining within the normal range.
Clinical features of hypothyroidism

Hypothyroidism is not easy to diagnose because its symptoms are found in a number of other diseases. Moreover, it often appears gradually and may produce very few, if at all, symptoms in younger adults. Generally, hypothyroidism is characterized by the slowing down of both physical and mental functions.

The clinical manifestations of hypothyroidism vary individually, depending upon the severity of hormonal dysfunction. It ranges from subclinical hypothyroidism (mildest) to the most severe form which is myxedema. In older people, they can be easily mistaken for stress and part of the natural aging process. The signs and symptoms during the early stages of the disease are (110):

- Intolerance to cold
- Constipation
- Fatigue
- Decreased perspiration
- Dry skin, itching
- Cramps in muscle
- Bradycardia
- Weight gain
- Depression
- Poor muscle tone
- Thin, brittle nails
- Menstrual irregularities

Myxedema coma

Myxedema coma is a severe life-threatening complication of hypothyroidism that usually presents with profound lethargy or coma accompanied with hypothermia. It affects multiple organs accompanied by progressive decline of mental function. There may be bradycardia, hypotension, and myxedema faces (dull, puffy, yellow skin, coarse hair, temporal loss of eyebrows, prominent tongue) (111).

Hypothyroidism in infant and children

Hypothyroidism in children is not common but it can affect them. This is especially true to those born to mothers with thyroid dysfunction. Early detection is very important as delayed treatment can seriously impact their physical and mental development. These days, babies are tested for hypothyroidism.

Hypothyroidism may be difficult to diagnose in infants since the presenting symptoms are quite general. These may include feeding difficulty, hoarse cry, slow activity, lethargy, thick tongue, swollen abdomen, constipation and increased sleep (110).

Symptoms of hypothyroidism in children vary individually, depending on the onset and present stage of the disease. Some common presentations are prolonged jaundice, enlarged thyroid gland, weight gain, slowness, learning difficulties, stunted growth or failure to grow and delayed puberty (110).

Autoimmune hypothyroidism

Autoimmune hypothyroidism is most often associated with Hashimoto’s thyroiditis or chronic thyroiditis. The autoimmune destruction of the thyroid gland gradually slows down or interferes with its metabolic functions.

Patients with Hashimoto’s thyroiditis may present with goiter rather than symptoms of hypothyroidism. The goiter may not be large but is usually irregular and firm in consistency. It is usually palpable upon physical examination. It is rare for uncomplicated Hashimoto’s thyroiditis to be associated with pain.

Patients with atrophic thyroiditis or late stage Hashimoto’s thyroiditis present with obvious epidermal signs and symptoms of hypothyroidism. The skin may be dry accompanied by decreased sweating, thinning of the epidermis, hair loss, and skin thickening without pitting (myxedema) (112).

Subacute thyroiditis (de Quervain’s thyroiditis)

Subacute thyroiditis or de Quervain’s thyroiditis usually succeeds recent viral infections. As a result, its clinical presentation is sometimes difficult to distinguish from pharyngitis because of their similarities. The patient may have upper respiratory catarrh in the

Additional symptoms such as constipation, difficulty concentrating or thinking, goiter, fatigue, heavy and irregular menstruation, cold intolerance, joint stiffness, and mild weight gain. Late in the disease, patients usually develop shrunken thyroid glands.

Reidel’s thyroiditis is a rare cause of chronic thyroiditis. The onset of disease is insidious with painless goiter and local pressure symptoms. Thyroid dysfunction is uncommon. Goiter is hard, non-tender, fixed and asymmetrical.

Another less common form thyroiditis is acute thyroiditis. It is usually due to bacterial infection, rather than an autoimmune response. There is painful swelling in the anterior neck, fever, and local pressure symptoms like dysphagia if associated with upper respiratory or systemic infection. The patient may remain euthyroid but sometimes, transient hormonal dysfunction may occur.
primary week with fever and pain in the thyroid area. The disorder is self-limiting. Due to the leakage of thyroid hormones in the initial stages, some of the symptoms may be suggestive of a hyper metabolic state. Depending upon the stage of the disease, the patient may have symptoms of either thyrotoxicosis or hypothyroidism.

**Clinical features of hyperthyroidism**

Hyperthyroidism results from the overactivity of the thyroid gland while thyrotoxicosis is the result of thyroid hormone excess in the blood. Both terms are often used interchangeably. The major etiology of thyrotoxicosis involves hyperthyroidism caused by Graves disease (toxic diffuse goiter), toxic multinodular goiter and toxic adenomas.

Primary thyrotoxicosis involves the diffuse enlargement of the thyroid gland accompanied by signs of hyper-metabolism with ocular dysfunctions that may or may not be present (Graves disease). It is the result of excess T4 and/or T3 secretion secondary to abnormal thyroid stimulation, thyroid hyperfunctioning nodules, or ectopic malignant thyroid hormone secretion. Secondary thyrotoxicosis is the result of excess TSH and T4 secretion due to nodular goiters (single or multiple).

Below is a table of the signs and symptoms of thyrotoxicosis (113).

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Sign</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nervousness and anxiety</td>
<td>Systolic hypertension</td>
</tr>
<tr>
<td>Heat intolerance</td>
<td>Warm, moist skin</td>
</tr>
<tr>
<td>Hyperactivity</td>
<td>Weight loss</td>
</tr>
<tr>
<td>Palpitations</td>
<td>Tachycardia</td>
</tr>
</tbody>
</table>

Clinical presentation depends on the severity of thyrotoxicosis, duration of the disease, individual susceptibility to thyroid hormone stimulation, and the patient’s age. In the elderly, symptoms of hyperthyroidism may be subtle or masked by existing comorbidities such as Alzheimer’s disease. The patient most often present with fatigue and weight loss.

The table below summarizes the most common presenting signs and symptoms per age group (113).

<table>
<thead>
<tr>
<th>Young patients</th>
<th>Elderly patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sympathetic activation such as anxiety, hyperactivity and tremor</td>
<td>Cardiovascular symptoms such as dyspnea, weight loss and atrial fibrillation</td>
</tr>
</tbody>
</table>

The symptoms of early onset hyperthyroidism are anxiety, tremulousness, generalized weakness, weight loss with increased appetite, diarrhea, oligomenorrhea, loss of libido, heat intolerance, skin tanning, pruritus, palpitation, irregular beats, shortness of breath, hyperactivity, muscle weakness, apathy in older age, anterior neck enlargement and pressure symptoms, stare, gritty sensation, increased lacrimal secretion, diplopia, and diminished visual acuity (113).

The signs of early onset hyperthyroidism are restlessness, inability to keep still, objective weight loss, excessive sweating, thinning and straightening, tachycardia, increased pulse pressure, ectopic beats, atrial fibrillation in elderly, sick sinus syndrome, cardiac failure, fine tremors, hyperreflexia, proximal muscle weakness, periodic paralysis, gynecomastia, diffuse or nodular goiter, bruit, thrill, lid retraction, lid lag, chemosis, infiltrative ophthalmopathy, ocular muscle paresis, and exposure keratitis (113).

**Thyroid storm**

Thyroid storm is rare but is considered one of the most severe manifestations of hyperthyroidism. It is a result of untreated hyperthyroidism but may also be precipitated by infection, trauma, surgery and diabetic ketoacidosis.

The signs and symptoms of a thyroid storm include fatigue, high grade fever, tachycardia, dyspnea, restlessness, confusion, psychosis, and coma. Patients with thyroid storm may see their condition progress to cardiovascular collapse and shock. Atrial arrhythmias are common. Thyroid storm is a medical emergency and is diagnosed based on clinical symptoms rather than on laboratory results (114).

**Nodular goiter**

Toxic nodular goiter such as those in Graves disease grows from an existing simple goiter. It may present as circumscribed area of firmness with regular margin that is the palpable nodule in the thyroid gland. It is usually more than 1 cm, as nodules smaller than this size are harder to palpate with certainty.

The size, symmetry, contour, consistency and mobility of the thyroid nodule and extranodular thyroid tissue should be defined. Thyroid nodules may be solitary or multiple and functional or nonfunctional.

Generally, thyroid nodules may be benign or malignant. The most effective way of initially differentiating between the two is conducting a thorough assessment of the patient history, laboratory and physical exam results. Particularly, the following points are taken into consideration:

1. Pattern of enlargement, duration and rate of growth. Short duration and rapid enlargement are consistent with neoplasm.
2. Associated local symptoms. Pain, dysphagia, dyspnea or hoarseness of voice suggests extrathyroidal tissue involvement.
3. Symptoms referring to hormonal status. Malignant nodules are not usually associated with hypothyroidism or hyperthyroidism. Medullary carcinoma may be associated with hyperparathyroidism and/or pheochromocytoma.

Physical examination should demarcate the dimensions of the thyroid nodule, whether it is single or multiple, the regularity of its margins, consistency and movement to adjacent structures. A solitary nodule is more likely to be malignant than multiple ones. Ill-defined margins, hardness and immobility are other characteristics of malignancy.

**Graves disease**

Patients with Graves disease (diffuse toxic goiter) may present with exophthalmoses, retraction of upper eye-lid and lid lag (thyroid stare). Graves disease is characterized by diffuse goiter, thyrotoxicosis, infiltrative orbitopathy and ophthalmopathy. Ophthalmopathy may be present with the following symptoms, blurring of vision, double vision, photophobia, increased lacrimation. Additionally, skin problems may also arise such as pretibial myxedema (115).
Nontoxic multinodular goiter

Most patients with nontoxic multinodular goiter are asymptomatic. Usually the goiter develops over many years and finally detected on routine examination. Sometimes, when the goiter has grown very large, it compresses nearby structures resulting in symptoms such as dysphagia and dyspnea. There may be sudden pain which is attributed to the presence of hemorrhage into the nodule. Sometimes, the laryngeal nerve is affected, leading to voice hoarseness.

Toxic multinodular goiter

Plummer disease is a form of toxic multinodular goiter. All the symptoms of goiter are present which may include subclinical hyperthyroidism or mild thyrotoxicosis. The patient may present with palpitations, tachycardia, tremor, and weight loss and atrial fibrillation in the elderly.

Hyperfunctioning solitary nodule

Mild hyperfunctioning solitary nodule of nonmalignant origins presents as a palpable thyroid nodule in the absence of clinical features suggestive of Graves disease or other causes of thyrotoxicosis. There may sometimes be mild thyrotoxicosis.

Thyroid cancer

The signs and symptoms of thyroid cancers will be discussed individually according to their classification below:

1. Well differentiated (good prognosis)
   a. Papillary
      ■ Minimal thyroid cancer
      ■ Invasive
   b. Follicular
2. Medullary (from parafollicular cells)
3. Anaplastic (undifferentiated)
4. Lymphoma
5. Others (metastatic, epidermoid, teratoma, sarcoma)

Papillary carcinoma

The size of the tumor varies significantly from microscopic to several centimeters located at the center of the front of the neck. Most of these lesions are very small and spread via the lymphatic system. Metastasis can also occur via the hematogenous route particularly to the nearby anatomical structures such as the bones and lungs. Additionally, these tumors may be multifocal and exhibit relatively slow growth and proliferation. Most of the time, there are no other symptoms.

Follicular carcinoma

The tumor varies from a well-differentiated, virtually normal-appearing thyroid tissue to nearly solid sheets of follicular epithelium with sparse evidence of follicular formation. Follicular carcinoma tends to metastasize by the hematogenous route affecting the bones, lungs and the central nervous system.

Anaplastic carcinoma

In microscopic examination, anaplastic carcinoma is characterized by poorly differentiated cells with very aggressive proliferation, spreading fast to the neck and other parts of the body (distant metastasis). The tumor often extends locally and may result in tracheal compression.

Medullary carcinoma

Medullary carcinoma produces and releases excess thyrocalcitonin and a protein called carcinoembryonic antigen (CEA) into the blood. It is often without varying endocrinopathy. There are usually bilateral lesions associated with pheochromocytoma and hyperparathyroidism.

Thyroid lymphoma

Thyroid lymphoma is usually of the nodular histiocytic form of thyroid cancer. It often arises from the background of Hashimoto’s thyroiditis. A rapidly expanding thyroid mass is its characteristic feature and suggestive of its diagnosis. A confirmed diagnosis is often possible only after open biopsy. Such tumors are radiosensitive.

Neuromuscular manifestations

Aside from cardiovascular, epidermal, endocrine, and physical signs and symptoms, thyroid disorders manifest with neurological manifestations that should be considered by clinicians when suspecting a thyroid dysfunction diagnosis since these are often masked by symptoms of other diseases. This is especially true in elderly patients because of the natural decline of bodily functions due to the aging process. Thyroid disorders have protean clinical presentation with a variety of symptoms involving multiple systems of the body. Thyroid hormone plays a significant role in the development and functioning of central and peripheral nervous system. Abnormalities in production and release of thyroid hormones therefore lead to neurological manifestations. In some forms of thyroid disorders, the neurological signs and symptoms may be the only presentation of the disease. These are discussed in detail below.
**Hypothyroidism**

1. Headache: Headache is a commonly encountered symptom in hypothyroidism. It usually presents as a headache of unknown causes. The underlying cause is attributed to the increased intracranial pressure brought on by hypothyroidism. In pediatric patients, subclinical hypothyroidism is associated with worsening of migraine headaches (120).

2. Dizziness and tinnitus: Both are very common in hypothyroidism. In fact, they are often the earliest symptoms. Tinnitus usually resolves once the thyroid levels normalize.

3. Hashimoto encephalopathy (HE): Current evidence shows that encephalopathy develops in steroid-responsive autoimmune thyroid disease (121). It is categorized into two types, namely:
   - First type: Characterized by acute episodes with transient focal neurological deficits and epileptic seizures.
   - Second type: Characterized by gradual onset of progressive dementia, followed by psychosis and coma after several weeks. In this type, no focal neurological deficits are seen.

4. Psychoneurological symptoms: These are the most common symptoms of hypothyroidism. These are mainly depressive symptoms, with major depression an often seen presenting feature. Additionally, other symptoms like mood swings, anxiety and even the myxedema madness may be seen (121).

**Hyperthyroidism**

1. Psychoneurological symptoms: It includes anxiety, restlessness, cognitive difficulties, and psychotic symptoms. Patients may also experience major depression (121).

2. Neuromuscular: Almost 80 percent of hyperthyroidism patients have neuromuscular complaints, with 50 percent of those experiencing muscular weakness. Generally, myopathy starts proximally, usually at the pelvic girdle then progress to the distal muscles (121). Myalgia, fatigue and exercise intolerance are common findings in these patients. Additionally, they may often feel breathless, due to the involvement of respiratory smooth muscles. Tendon reflexes remain normal.

3. Thyrotoxic periodic paralysis: It manifests as recurrent episodes of hypokalemia and muscular weakness that lasts for days. The incidence is more common among males, with 11:1.2 male to female ratio. The paralytic attack starts with symptoms such as pain, cramping, stiffness followed gradually by paralysis. The attack may last up to 48 hours. Proximal muscles are more severely involved than the distal ones (121).

4. Exophthalmic ophthalmoplegia: This is otherwise known as Graves ophthalmopathy. There are two existing types (121):
   - Functional abnormality: This is due to overactivity of the sympathetic nervous system.
   - Infiltrative ophthalmopathy: This involves the orbital contents which presents serious outcomes. Additionally, ocular muscle paralysis is also seen in many patients. It results in the appearance of protruded eyeballs from its sockets, a typical diagnostic feature of Graves disease. Strabismus and diplopia are other ocular manifestations as well as pain and lid retraction. An increase in intraocular pressure and damage to the optic nerve are among the other manifestations of hyperthyroidism.

5. Myasthenia gravis: It is also an autoimmune disorder which often coexists with hyperthyroidism. Patients with myasthenia gravis have higher risk of developing hyperthyroidism. Fatigue is the main presenting symptom (121).

**DIAGNOSIS**

**Physical exam**

Usually, thyroid disorders are discovered during routine physical exam. A clinician inspects and palpates the neck using the hands. If a palpable nodule in the anterior part is found, the clinician may possibly ask about the medical history such as radiation therapy and risk factors including family history.

Additionally, clinicians will note the gland texture, mobility and tenderness of nodules, if any.

**Thyroid function tests**

The most accurate way to assess thyroid function is through blood tests measuring the TSH, anti-thyroid antibody and calcitonin levels. Another test, a more reliable type, done to assess the thyroid status is the measurement of free T4 (fT4) in the blood. The fT4 and fT3 provide more accurate readings of T4 and T3 levels, respectively.

According to the Journal of the American Medical Association (JAMA), screening adults who are more than 35 years old for mild thyroid failure is as cost-effective as screening for high cholesterol or high blood pressure (124).

Following is a table of the summary of the various thyroid function tests and their reference values. Each one is discussed in detail in the succeeding pages.
The secretion of TSH is governed by the reduction and elevation of thyroid hormones. TSH levels can vary from day to day by up to about 50 percent. Hypothyroidism can have drawbacks, namely:

- Over-secretion of thyroid hormones (hyperthyroidism). Occasionally, low TSH level usually suggest an overactive thyroid and over-secretion of thyroid hormones (hyperthyroidism). On the other hand, low TSH level usually suggest an overactive thyroid and over-secretion of thyroid hormones (hyperthyroidism). Occasionally, the upper normal of serum TSH levels is 4.5 mIU/L. A “reference population” taken from the disease-free population made up of non-pregnant, those with negative lab findings for hyperthyroidism or hypothyroidism, lacked detectable thyroidglobulin antibodies or thyroid autoantibodies, and were not on estrogens, androgens, or lithium exhibited an upper normal TSH value of 4.12 mIU/L. This finding was backed by the Hanford Thyroid Disease Study, which analyzed a cohort without evidence of thyroid disease, were seronegative for thyroid autoantibodies, were not on thyroid medications, and had normal thyroid ultrasonographic examinations which did not disclose nodularity or evidence of thyroiditis (228).

A reduction of thyroid hormone levels leads to increase in the size and number of the thyroid follicular cells, an increased TRH and TSH secretion, and thus, stimulation of thyroid hormone synthesis and release. Elevated thyroid hormone levels stimulate the breakdown of TRH, resulting in the reduced number of TRH receptors on pituitary cells, and inhibition of the pituitary response to TRH stimulation. The overall result is reduced production and release of TSH until T3 and T4 levels normalize (123).

Due to the high binding affinities of T4 and T3, only a very small portion of the free physiologically active hormones circulates in the blood. It is worth noting that the concentration of proteins that bind T4 and T3 vary widely between euthyroid individuals, making such measurements inconsistent and sometimes, unreliable. Unbound T4 and T3 (FT3 and FT4) provide a better hint of the patient’s thyroid function than the total T3 and T4 levels. FT4 and FT3 are usually used to verify abnormal thyroid status indicated by the initial TSH screening test (123).

As mentioned earlier, the thyroid gland secretes two iodine-containing hormones, T4 and T3. It produces more T4, which when released is converted in the peripheral tissues to T3, the more active hormone. The production and secretion of T4 and T3 are stimulated TSH which is secreted by the anterior pituitary gland. In turn, the release of TSH is stimulated by the hypothalamic hormone, thyrotropin releasing hormone (TRH). Both T4 and T3 produce a negative feedback effect on the pituitary and hypothalamus, regulating the TSH and TRH release, respectively. TSH is a good index of thyroid function and is recommended as the primary screening test for suspected thyroid diseases (123).

In most cases, the initial test conducted to assess thyroid function is the measurement of TSH level in a blood sample. The rationale behind this is to first determine whether TSH is suppressed, normal or elevated. Below is a summary of the implication of each result.

### TSH test

<table>
<thead>
<tr>
<th>Decreased TSH</th>
<th>Normal TSH</th>
<th>Elevation of TSH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overactive thyroid gland: Hyperthyroidism, secondary hypothyroidism</td>
<td>Normal thyroid gland</td>
<td>Failing thyroid gland: Primary hypothyroidism</td>
</tr>
</tbody>
</table>

Elevated TSH level suggests failure of the thyroid gland due to direct deleterious effects (primary hypothyroidism). On the other hand, low TSH level usually suggest an overactive thyroid and over-secretion of thyroid hormones (hyperthyroidism). Occasionally, the upper normal of serum TSH levels is 4.5 mIU/L. A “reference population” taken from the disease-free population made up of non-pregnant, those with negative lab findings for hyperthyroidism or hypothyroidism, lacked detectable thyroidglobulin antibodies or thyroid autoantibodies, and were not on estrogens, androgens, or lithium exhibited an upper normal TSH value of 4.12 mIU/L. This finding was backed by the Hanford Thyroid Disease Study, which analyzed a cohort without evidence of thyroid disease, were seronegative for thyroid autoantibodies, were not on thyroid medications, and had normal thyroid ultrasonographic examinations (which did not disclose nodularity or evidence of thyroiditis) (228).

### Shortcomings of the TSH test

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anti-thyroid antibody status, and urinary iodine showed insignificant
effects on these measurements (229).
4. The National Academy of Clinical Biochemists indicated that 95
percent of persons lacking clinical findings for thyroid disease
have TSH concentrations under 2.5 mIU/L (230), and suggested
the lowering of the upper limit of the TSH reference to 2.5 mIU/L
(231). While many patients with TSH concentrations in the said
range do not necessarily progress to hypothyroid states, those
patients with autoimmune thyroid disease have higher chances of
developing hypothyroidism that may be subclinical or overt (232).
5. Patients without laboratory evidence of autoimmune thyroid
disease may have TSH measurements over 3.0 mIU/L, with
incidence that increases with age, with elderly (>80 years of
age) individuals having a 23.9 percent prevalence of TSH values
between 2.5 and 4.5 mIU/L, and a 12 percent prevalence of
TSH levels above 4.5 mIU/L (233). Therefore, very mild TSH
elevations in the elderly may not always indicate an underlying
subclinical thyroid disorder, but rather a normal part of the aging
process. The prerequisite is that while the normal TSH reference
range—particularly for some subpopulations—may need to be
narrowed (230), the normal reference range may broaden with
advancing age (229). Thus, not all patients who have mild TSH
elevations are hypothyroid and require hormone replacement.
6. Serum TSH may become abnormal in other euthyroid states such
as TSH suppression in inpatients with acute illness, and levels
below 0.1 mIU/L in combination with subnormal fT4 levels may
be found in patients with critical illnesses, especially in those
being administered with dopamine infusions (234).
7. Patients receiving pharmacologic doses of glucocorticoids may also
experience abnormally low TSH measurements (235). Moreover,
TSH levels may be elevated, but generally under 20 mIU/L during
the recovery phase from non-thyroidal illness (236). Therefore, there
are limitations to TSH measurements in inpatients and must only be
ordered when thyroid dysfunction is strongly suspected (237).

T4 tests
Circulating T4 exists in two forms (125):
1. T4 that is bound to carrier proteins that disables its entry into body
tissues that may require it and,
2. Free T4 (fT4) freely enters the body tissues to exert its
physiological actions. The fT4 fraction is most important in
determining the status of thyroid function; the tests used to
measure this are called the free T4 (fT4) and the free T4 Index
(fT4I or FTI).
Measurements of fT4 and fT3 have largely replaced the need for
measurement of total T4 and total T3 levels.
If TSH level is abnormal, fT4 is employed to arrive at a conclusive
diagnosis. Patients with hyperthyroidism will either have an elevated
fT4 or FTI, whereas patients with hypothyroidism will either have a
decreased fT4 or FTI levels. Combining the TSH test with the fT4 or
FTI accurately establishes thyroid function.
The finding of an elevated TSH and low fT4 or FTI indicates primary
hypothyroidism. It occurs when the pituitary gland recognizes the
underactivity of the thyroid gland and in response, releases more TSH
in an effort to stimulate it to produce thyroid hormones. If the thyroid
gland is functioning normally, it will not react to the stimulation,
leading to elevated TSH levels with low fT4 levels. Low TSH and low
fT4 or FTI indicates hypothyroidism due to a dysfunctional pituitary
gland, a condition called secondary hypothyroidism. A low TSH with
an elevated fT4 or FTI is found in individuals with hyperthyroidism.

T3 tests
T3 is tested in cases of hyperthyroidism where the T4 levels are
within the normal range. T3 tests are especially helpful in diagnosing
hyperthyroidism or determining its severity. Patients who are
hyperthyroid will have increased T3 levels. In some individuals with
low TSH, only the T3 level is increased and the fT4 or FTI levels remain
normal. Measuring T3 levels is not useful in the hypothyroid patient,
since it is the last test to show abnormalities. For example, patients may
experience severe hypothyroidism with an elevated TSH and decreased
fT4 or FTI levels, but show normal T3 levels. In other scenarios such as
during gestation or while on contraceptives, elevated levels of total T4
and T3 can happen. This is because the estrogens increase the binding
protein levels. In these cases, it is better to request for both TSH and fT4
for an accurate evaluation of the thyroid function (125).
In hypothyroidism caused by pituitary disease where the TSH remains
within normal range or one which develops within 12 months of
treatment for thyrotoxicosis, the TSH value remains suppressed in
individuals who are thyroid hormone resistant. In these cases, testing
of free thyroid hormones is recommended in addition to the TSH.
If TSH level is abnormally low, a fT4 or fT3 assay should be obtained,
and in difficult cases when the suspicion of thyroid dysfunction
remains high, a combination of all three tests (TSH, fT3, fT4) is
usually enough to prevent misdiagnosis.

Six Clinical Patterns of Thyroid Function Tests

<table>
<thead>
<tr>
<th>Common</th>
<th>Less Common</th>
<th>Rare</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary hyperthyroidism</td>
<td>Transient thyroiditis</td>
<td>Ectopic thyroid tissue</td>
</tr>
<tr>
<td>Graves’ disease</td>
<td>Postpartum</td>
<td>Iodine-induced</td>
</tr>
<tr>
<td>Multinodular goiter</td>
<td>Post-viral infections (granulomatous, subacute, De quervain’s)</td>
<td>Gestational thyrotoxicosis (Positive pregnancy test)</td>
</tr>
<tr>
<td>Toxic nodule</td>
<td>Hydatidi-formmole (Positive pregnancy test)</td>
<td>Familial-gestational hyper-thyroidism (Positive pregnancy test)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Common</th>
<th>Rare</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subclinical hyperthyroidism</td>
<td>Steroid therapy</td>
</tr>
<tr>
<td>Thyroxine ingestion</td>
<td>Dopamine and dobutamine infusion</td>
</tr>
<tr>
<td>Non-thyroidal illness</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Common</th>
<th>Rare</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-thyroidal illness</td>
<td>Secondary hypothyroidism (pituitary disease)</td>
</tr>
<tr>
<td>Recent treatment for hyperthyroidism (TSH suppressed)</td>
<td>Congenital TSH deficiency</td>
</tr>
</tbody>
</table>
Inability to predict malignancy

- Its inability to provide any functional information of the thyroid
- Are three drawbacks associated with ultrasonography scans, namely:

  - Most common site of metastatic lymph node involvement (128). There associated lymphadenopathy, if any, in the paratracheal region, the
  - Of a nodule (127). Other advantages include the demonstration of differentiating cystic from solid lesions, determining nodularity,
  - Is effective at thoroughly tracing the intra-thyroidal architecture, noninvasive, and requires no radiation exposure. Ultrasonography

Once a thyroid nodule is palpated, the first imaging modality ordered by clinicians to corroborate lab test results and physical findings is ultrasonography. It is readily available, cost-effective, and noninvasive, and requires no radiation exposure. Ultrasonography is effective at thoroughly tracing the intra-thyroidal architecture, differentiating cystic from solid lesions, determining nodularity, and accurately pinpointing the exact location and measurement of a nodule (127). Other advantages include the demonstration of associated lymphadenopathy, if any, in the paratracheal region, the most common site of metastatic lymph node involvement (128). There are three drawbacks associated with ultrasonography scans, namely:

- Its inability to provide any functional information of the thyroid gland
- Inability to predict malignancy

The test is initially done by the administration of a small amount of radioactive iodine by the patient. Once inside, the clinician uses the radioactivity of the iodine to measure the amount of iodine molecules being absorbed or taken in by the thyroid gland.

Radioactive iodine uptake test (RAIU)

Remember that thyroid hormones including T4 contain iodine. The thyroid gland needs to acquire high iodine amounts from the blood so it can synthesize the amount of T4 required by the body to function normally. This is the activity that is being measured by the radioactive iodine uptake test.

The test allows clinicians to establish the functional status of the thyroid gland. A very high RAIU is normally observed in patients with hyperthyroidism while a low RAIU is observed in patients with hypothyroidism. The normal results are outlined in the table below (126):

<table>
<thead>
<tr>
<th>Time</th>
<th>% of T4 uptake</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 hours</td>
<td>3-16%</td>
</tr>
<tr>
<td>24 hours</td>
<td>8-25%</td>
</tr>
</tbody>
</table>

Moreover, the clinician may opt to follow up this test with a thyroid scan to allow full visualization of the thyroid gland.

RADIOPHASIC IMAGING MODALITIES

- Dependence on the ultrasonographer for the quality of images, areas of the neck covered, and interpretation of the results

In the recent years, there have been features added to the ultrasonographic scanning techniques to enable the identification of a higher risk of malignancy within a nodule, including microcalcifications and central blood flow (129). Sequential ultrasonographic scans allow clinicians to monitor disease progression, assess therapeutic outcomes, and identify recurrence.

It should be noted that ultrasonography results can be misleading if lateral neck nodal areas are not fully inspected for nodal disease (130).

4. Raised TSH, low fT4 or fT3 (Primary hypothyroidism)

<table>
<thead>
<tr>
<th>Common</th>
<th>Rare</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic autoimmune thyroiditis</td>
<td>Iodine excess</td>
</tr>
<tr>
<td>Post thyroidectomy</td>
<td>Riedel's thyroiditis</td>
</tr>
<tr>
<td>Hypothyroid phase of transient thyroiditis</td>
<td></td>
</tr>
</tbody>
</table>

5. Raised TSH, normal fT4 or fT3

<table>
<thead>
<tr>
<th>Common</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subclinical autoimmune thyroiditis</td>
</tr>
</tbody>
</table>

6. Normal or raised TSH, raised fT4 or fT3

<table>
<thead>
<tr>
<th>Rare</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resistance to thyroid hormone</td>
</tr>
<tr>
<td>TSH secreting pituitary tumor</td>
</tr>
<tr>
<td>Acute psychiatric illness</td>
</tr>
</tbody>
</table>

Thyroid antibody tests

Elevated anti-thyroglobulin and anti-microsomal antibody titers are seen in autoimmune diseases such as chronic lymphocytic (Hashimoto’s) thyroiditis (hypothyroid cases), and lymphadenoid goiter (euthyroid cases). Recent evidence indicates thyroid peroxidase to be the microsomal antigen present in the serum of patients with Graves disease or Hashimoto’s thyroiditis.

The two major antibodies, thyroid peroxidase and thyroglobulin, are implicated in autoimmune thyroid disorders and cause destruction of thyroid cellular proteins. Monitoring thyroid antibodies levels helps in the diagnosis of thyroid disorders. For instance, a positive anti-thyroid peroxidase (anti-TPO), previously referred to as thyroid antimicrosomal antibodies and/or anti-thyroglobulin antibodies, in a patient with hypothyroidism is a diagnosis of Hashimoto’s thyroiditis. Generally speaking, a positive finding for antibodies in a hyperthyroid patient is most likely seen in the presence of an autoimmune thyroid disease (125).

The inactive metabolite of T4 is called the reverse T3, 3, 5, 5'-triiodothyronine (rT3). During acute febrile illnesses, chronic hepatic cirrhosis, and other miscellaneous chronic systemic illnesses, its level increases, especially in infants. These patients will exhibit low T3 levels even at euthyroid states because T4 is deiodinated to rT3 rather than T3. Measuring rT3 levels in amniotic fluid might be a helpful tool in assessing fetal thyroid function because rT3 is the major metabolite of T4 in the fetus. The serum reference ranges for rT3 in adults and children are 30 - 80 and 20 - 70 ng/dL, respectively (123).

Thyroglobulin

Thyroglobulin (Tg) is a glycoprotein produced by both normal and cancerous thyroid cells. It does not measure thyroid function nor diagnose thyroid carcinoma in the presence of an intact thyroid gland. It is most useful in the postoperative monitoring of patients who underwent thyroidectomy for thyroid carcinoma. If the whole thyroid is removed, a procedure called total thyroidectomy, the Tg level normally reads at zero. Tg does not assess thyroid hormone function (123).

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Moreover, the clinician may opt to follow up this test with a thyroid scan to allow full visualization of the thyroid gland.

Ultrasonography (US)

- Dependence on the ultrasonographer for the quality of images, areas of the neck covered, and interpretation of the results

In the recent years, there have been features added to the ultrasonographic scanning techniques to enable the identification of a higher risk of malignancy within a nodule, including microcalcifications and central blood flow (129). Sequential ultrasonographic scans allow clinicians to monitor disease progression, assess therapeutic outcomes, and identify recurrence.

It should be noted that ultrasonography results can be misleading if lateral neck nodal areas are not fully inspected for nodal disease (130).
Other imaging modalities

CT and MRI imaging modalities are used in cases suggestive of thyroid carcinoma. CT is especially effective in the identification and outlining of the full extent of cervical lymphadenopathy and the relationship of the thyroid gland to its surrounding cervical tissues. It has been found that the use of contrast CT in the assessment of thyroid carcinoma linked to short delays in scanning and radioiodine therapy for up to 6 to 8 weeks. Because of this very reason, this modality should be used judiciously and appropriately (131).

Contrast CT is best used in patients with associated lymphadenopathy on physical exam or ultrasonography and in patients with positive papillary thyroid carcinoma in their fine needle aspiration test. These findings usually require the clinician to expect significant nodal disease and use aggressive radiographic evaluation techniques. The use of ultrasonography combined with CT in these situations allows clinicians to evaluate the central and lateral neck nodes accurately as well as the thyroid gland’s relationship to the central neck viscera. The radiographic combination produces a well-defined preoperative nodal map that allows clinicians to direct nodal dissection during surgery. The additional accuracy enables clinicians to perform comprehensive nodal resection at first surgery, which is of greater therapeutic value to papillary cancer patients than prompt postoperative radioiodine therapy (131).

The image resolution, standard illustration of neck anatomy, and relative ease of interpretation of CT make it an ideal modality for preoperative assessment in patients with fine needle aspiration results that is positive for papillary cancer.

MRI can also be used for the assessment of the thyroid gland by employing a neck or surface coil which provides excellent soft tissue resolution, with nodules as small as 4 mm being detected (132).

Fine-Needle Aspiration Biopsy (FNAB) or FNA

Fine needle aspiration biopsy is the gold standard in making the decision whether to opt for surgical treatment of thyroid carcinoma. Its sensitivity and specificity for thyroid carcinoma are high, approximately at 65-98 percent and 72-100 percent, respectively, making it the first choice for routine diagnosis and management of thyroid nodules (133) (134) (135).

FNAl results are grouped into four main cytological categories, namely; benign, malignant, indeterminate (suspicious), and non-diagnostic (unsatisfactory). The table summarizes the possible findings in each group. The implications of the findings of each group are central to the appropriate management of the disease (136).

<table>
<thead>
<tr>
<th>Category</th>
<th>Benign cysts</th>
<th>Colloid nodules</th>
<th>Thyroiditis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benign</td>
<td>Nondiagnostic</td>
<td>Suspicious</td>
<td>Suspicious</td>
</tr>
<tr>
<td>Malignant</td>
<td>Nondiagnostic</td>
<td>Suspicious</td>
<td>Suspicious</td>
</tr>
<tr>
<td>Indeterminate (suspicious)</td>
<td>Nondiagnostic</td>
<td>Suspicious</td>
<td>Suspicious</td>
</tr>
<tr>
<td>Nondiagnostic</td>
<td>Nondiagnostic</td>
<td>Suspicious</td>
<td>Suspicious</td>
</tr>
</tbody>
</table>

Benign: It is the most common result, representing about 70 percent of cases. Surgical intervention is not warranted. If the nodule grows or displays worrisome clinical characteristics, a repeat FNA or surgery should be considered. This classification includes a benign macrofollicular adenoma, multinodular goiter, or thyroiditis (137).

Malignant: Malignancy represents approximately only 4 percent of cases. Papillary thyroid carcinoma (PTC) is the most common result because of its diagnostic nuclear features that allows cytological diagnosis. However, there are certain cases where these nuclear features are seen but are insufficient to confirm a diagnosis of PTC and classified only as suspicious. This classification includes medullary carcinoma and highly malignant carcinomas (anaplastic carcinomas and high-grade metastatic lesions) (138) (139).

Suspicious: Aspirates with indeterminate results are labeled as suspicious. It represents about 10 percent of all FNA results. Findings include invisible vascular or capsular invasion on a cytological sample that is commonly associated with follicular neoplasms and Hürthle cell neoplasms. PTCs may also be part of this classification when some nuclear features are seen, but cytological evidence is insufficient to make a definitive diagnosis. There are several factors that increase the probability of malignant follicular neoplasms, namely (140):
- Nodule size greater than 4 cm
- Solitary nodule
- Male sex
- Fixed nodule on palpation

If the aspirate is strongly suspected for PTC, a hemithyroidectomy can be performed and sent for frozen section. If the frozen section confirms it, a complete thyroidectomy is then performed. Patients are advised preoperatively about the surgery; with the frozen section being only a representative sample of the tumor, with the possibility of the final pathology being different from the frozen sample obtained. Due to the nature of follicular thyroid carcinoma and Hurthle cell carcinoma, a diagnosis using this approach cannot be done. Therefore, when follicular or Hurthle cell neoplasms are strongly suspected, the best surgical option is to perform hemithyroidectomy minus the frozen section succeeded by a complete thyroidectomy if the final pathology is confirmed for malignancy.

Non-diagnostic: Non-diagnostic aspirates are samples that provide insufficient cytological material for a confirmed diagnosis. Patients should be made aware of the result being neither positive nor negative; that no diagnostic material was found in the sample obtained. In cases where two consecutive FNA resulted in nondiagnostic findings, a surgical excision may be a reasonable alternative.

US-Guided FNA

US-guided FNA is helpful in small nodules, usually <1.5 cm or when a previous aspiration attempt was unsuccessful. Studies have shown that a diagnosis was achieved in 91.5 percent of cases when US-guided FNA was employed compared with 85.9 percent of cases when palpation alone was employed (141).

TREATMENT

Treatment approaches vary between individuals, depending on the type of disorder, comorbidities, severity and other factors. Treatment of thyroid disorders in general is extremely satisfying, as most patients can be either cured or have their diseases controlled.
Hypothyroidism

There is common consensus that patients with primary hypothyroidism with TSH levels over 10 mIU/L should be treated (142). However, there is less certainty about treatment protocols in patients with TSH levels of 4.5–10 mIU/L (143). There are a couple of initial studies done on patients with subclinical hypothyroidism (TSH levels between 2.5 and 4.5 mIU/L), that suggest beneficial response in reduction of atherosclerotic risk factors such as atherogenic lipids, impaired endothelial function, and intima media thickness. However, there are no solid clinical data supporting the treatment of such patients, with pregnant women as the only exception. Spontaneous miscarriage during the first and second trimesters of gestation and stillbirth later on in the pregnancy are associated with increase in anti-thyroid antibody-negative women with subclinical hypothyroidism.

Treatment of the hypothyroid patient is straightforward and consists of hormone replacement. The standard drug used is synthetic L-thyroxine sodium preparations which must be customized to the individual patient (144).

Because of the sensitivity of the dosage requirements, uniqueness of the various dosage formulations available in the market (e.g. liquid-containing capsules with the inactive ingredients gelatin, glycerin, and water) and uncertainty about true interchangeability among the various formulations, current guidelines encourage the use of one L-thyroxine preparation per patient throughout the duration of therapy to minimize variability between refills (146) (147). The daily dose of L-thyroxine depends on the patient’s age, sex, and body mass. When calculating doses, the ideal body weight is employed because lean body mass is the best predictor of daily drug requirements (147). L-thyroxine administered with water an hour prior to breakfast or at bedtime 4 hours after the last meal on an empty stomach exhibit superior absorption profiles. Although L-thyroxine is better absorbed when administered an hour before meals compared to half an hour before meals, patient adherence may be improved by instructing patients to consistently drink it with water between 30 and 60 minutes before breakfast.

L-thyroxine should not be taken with medications or food that interfere with its absorption and metabolism. The table below lists some of the most common ones.

Hyperthyroidism

Treatment of hyperthyroidism depends on its etiology, severity and other factors. When diagnostic work up points to thyroiditis as the underlying cause, symptomatic treatment is usually sufficient because of its transient nature. Graves disease, toxic multinodular goiter, and toxic adenoma can be treated with radioactive iodine ablation (treatment of choice in the US), anti-thyroid drugs, or thyroidectomy. The latter is an option when other treatments have failed or are contraindicated, or when a goiter compresses adjacent viscera and cause symptoms. Generally, the purpose of anti-thyroid drugs is to reduce thyroid activity and hormonal effects which are responsible for the presenting symptoms (151).

Special treatment approaches are considered in patients who are pregnant or breastfeeding, with Graves ophthalmopathy, and amiodarone-induced hyperthyroidism.

Special circumstances such as the presence of coexisting ophthalmopathy in patients with Graves disease may also influence the choice of therapy since radioactive iodine may aggravate the ophthalmopathy. Although younger patients with hyperthyroidism often can be treated effectively with radioactive iodine, medical therapy with anti-thyroid drugs to reduce thyroid hormone levels is preferred. In younger patients with very large goiters, thyroidectomy is a viable alternative. In older patients or those with cardiac disease, radioactive iodine usually is recommended after the patient has been rendered euthyroid with anti-thyroid medications. Recombinant human TSH is available for stimulation of radioactive iodine uptake (RAIU) and release of thyroglobulin in patients with thyroid cancer after thyroidectomy. It has mostly eliminated hypothyroidism after thyroid hormone withdrawal for patients who undergo a total body scan and serum thyroglobulin measurements to determine the presence of residual tissue.

Below is a table with key clinical practice recommendations with corresponding evidence ratings (151).

<table>
<thead>
<tr>
<th>Clinical recommendation</th>
<th>Evidence rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>The choice of radioactive iodine, antithyroid medication, or surgery for hyperthyroidism should be based on the cause and severity of the disease as well as on the patient’s age, goiter size, comorbid conditions, and treatment desires.</td>
<td>C</td>
</tr>
<tr>
<td>Total thyroidectomy is recommended only for patients with severe disease or large goiters in whom recurrences would be more problematic.</td>
<td>C</td>
</tr>
<tr>
<td>Nonselective beta blockers such as propranolol (Inderal) should be prescribed for symptom control because they have a more direct effect on hypermetabolism.</td>
<td>C</td>
</tr>
</tbody>
</table>

Bileacidsequestrants(cholestipol, cholestyramine) High fiber diet
Sucralfate Soybean
Ferrous sulfate Espresso coffee
Grapefruit juice Calcium salts found in multivitamins
Proton pump inhibitors (omeprazole) Chromium picolinate
H2 antagonists (ranitidine) Phosphate binders (sevelamer)

Patients who are unable to take L-thyroxine orally may be given 70 percent or less of their usual dose intravenously. Crushed tablets of L-thyroxine suspended in water can be administered through enteral feeding via NGT.

Patients with minimal thyroid dysfunction, a full replacement dose of approximately 1.6 μg/kg/day of L-thyroxine is usually sufficient while patients who underwent total thyroidectomy and/or radiiodine therapy and with central hypothyroidism may require higher doses. Patients with subclinical hypothyroidism or who underwent treatment for Graves disease may require a lesser dose. Young healthy adults can be started on full replacement dose. This treatment approach to initial therapy results in rapid normalization of serum TSH compared to lower doses. Both doses, however, provide similar time for symptom resolution (148). On the other hand, patients with subclinical hypothyroidism do not require full replacement doses. Instead, they may be given doses of 25–75 μg/kg/day to reach euthyroid levels, with the higher doses reserved for those with higher TSH values (149).

Nutraceuticals in the form of desiccated thyroid has not been systematically studied in the treatment of hypothyroidism. Absorption profiles of orally administered desiccated thyroid differ between brands and origins (e.g. porcine or bovine). L-triiodothyronine in combination with L-thyroxine is another treatment option in hypothyroidism.

A study by Adrees et al. strongly suggests that treatment of subclinical hypothyroidism can significantly reduce atherosclerosis (150).
The evidence rating is coined by the American Academy of Family Physicians. Each rating is discussed in detail below (151).

A = consistent, good-quality patient-oriented evidence
B = inconsistent or limited-quality patient-oriented evidence
C = consensus, disease-oriented evidence, usual practice, expert opinion, or case series

### Anti-thyroid drugs and other thyroid inhibitors

Anti-thyroid drugs and other thyroid inhibitors interfere, directly or indirectly, with the production, secretion, or physiological effects of T3 and T4. Some have been used for more than a decade to control hyperthyroidism. These drugs are grouped into four main classes:

1. **Anti-thyroid drugs which directly block thyroid hormone synthesis**
2. **Iodic inhibitors which inhibit the iodide transport system**
3. **Elevated levels of iodine to reduce thyroid hormonal synthesis and secretion**
4. **Radioactive iodine which kills cancerous cells with the use of ionizing radiation**

Adjuvant therapy with drugs that do not affect thyroid hormonal function is useful in controlling the clinical signs and symptoms of thyrotoxicosis. Specifically, these are inhibitors of peripheral conversion of T4 to T3, b-adrenergic receptor antagonists, and calcium channel antagonists (152).

### Anti-thyroid drugs

The anti-thyroid drugs with clinical value are the thioureylenes, which belong to the family of thionamides. Propylthiouracil (PTU) is its prototypical compound. Other commonly used anti-thyroid drugs currently are methimazole and carbimazole, the latter is a carboxethoxy derivative of methimazole which is converted to it after absorption.

Anti-thyroid drugs inhibit the formation of thyroid hormones by interfering with the incorporation of iodine into tyrosyl residues of thyroglobulin. They also inhibit the coupling of these iodotyrosyl residues to form iodothyronines. These inhibitory actions imply their interference with the peroxidase-mediated oxidation of iodide ion and iodotyrosyl groups. The anti-thyroid drugs bind to and inactivate the enzyme peroxidase only when the enzyme is in the oxidized state. Over a period of time, the inhibition of hormone synthesis results in the depletion of iodinated thyroglobulin stores as the proteins are hydrolyzed and the hormones released into the circulation (151).

Methimazole usually is the drug of choice in non-pregnant patients because of its cost-effectiveness, longer half-life, and reduced incidence of agranulocytosis. The initial dose is 15 to 30 mg per day which may be given with a beta blocker such as propranolol. The beta blocker can be tapered off after four to eight weeks and the methimazole adjusted, according to clinical status and monthly T4 or T3 levels, toward an ultimate euthyroid state requiring only maintenance doses of 5 to 10 mg per day (153) (154). TSH levels tend to remain undetectable for months after the normalization of thyroid hormone levels and should not be the test used to monitor therapy. At one year, if the patient shows clinical and biochemical normal accompanied by an undetectable thyroid-stimulating antibody level, therapy may be discontinued. However, if the latter is elevated, the clinician may need to consider continuing therapy for another year. While some patients respond well to therapy, there are also higher rates of relapses reported.

Drug-induced hypothyroidism indeed can develop in patients with mild hyperthyroidism taking high doses of methimazole. In contrast, insufficient doses can very well result to under treatment and unresolved hyperthyroidism. After initiation of therapy, the patient’s thyroid function needs to be monitored closely and tested regularly, preferably every four to six weeks until thyroid function has been restored. Usually, after 4 to 12 weeks of treatment, most patients show significant clinical improvements with some showing normal thyroid function, after which dose reduction may be considered to maintain normal thyroid function. Disease control is achievable with low doses, some patients showing thyroid function normalization at daily doses of 5 to 10 mg of methimazole or 100 to 200 mg of propylthiouracil. After the first three to six months, follow-up intervals can be increased to every two to three months and then to every four to six months.

In addition to blocking hormone synthesis, propylthiouracil partially blocks the peripheral conversion of T4 to T3. Methimazole does not exhibit the same actions; and though the significance of this inhibition has not been firmly understood, it gives a sound foundation for the preference of propylthiouracil over other anti-thyroid drugs in the treatment of severe hyperthyroidism or thyroid storm, where a reduced conversion rate of T4 to T3 is therapeutically beneficial. Propylthiouracil is the drug of choice in pregnant women since methimazole is associated with congenital abnormalities. Its initial dose is 100 mg thrice a day with a maintenance dose of 100 to 200 mg daily (155). Both propylthiouracil and methimazole are rapidly absorbed from the gastrointestinal tract.

When measured, the duration of organification of radioactive iodine by the thyroid gland will usually show an effective absorption rate of approximately 20 to 30 minutes following an oral dose of propylthiouracil. The inhibitory effect of a dose of 100 mg of propylthiouracil starts to decline at 2 to 3 hours, with its 500 mg dose being only effective for 6 to 8 hours after intake. A single dose of 10 to 25 mg is needed to maintain its minimum plasma concentration up to 24 hours.

The plasma half-life of propylthiouracil and methimazole are approximately 1.25 hours and 4-6 hours, respectively. The drugs accumulate in the thyroid gland; methimazole accumulates in the organ after carbimazole administration. Drugs and metabolites are excreted via the kidneys and appear mostly in urine.

### Side effects

The side effects associated with propylthiouracil and methimazole are relatively low. The development of agranulocytosis with methimazole is suspected to be dose-related; however, the same dose-response is not seen with the use of propylthiouracil.

The most common adverse reaction is a mild, occasionally purpuric, urticarial papular rash. It often subsides spontaneously without requiring treatment, but it sometimes calls for the administration of an antihistamine or changing to another drug. Other less frequent complications are pain and stiffness in the joints, paresthesias, headache, nausea, skin pigmentation, and loss of hair. Drug fever, hepatitis, and nephritis are rare, although abnormal liver function tests are often seen with higher doses of propylthiouracil (156).

**Symptoms of overdose may occur, namely:**
- Change in consciousness
- Cold, clammy skin
- Confusion
- Disorientation
- Fast or weak pulse
- Light-headedness
- Loss of consciousness
- Sudden headache
after radioactive iodine treatment, clinicians often require patients to undergo spontaneous remission. Since therapeutic outcomes are not seen right away, patients with toxic nodular goiter, since the disease does not go into remission. Finally, it is also indicated in the case of partially thyroidectomized patients and when prolonged treatment with anti-thyroid drugs has not led to remission. It is the best form of treatment when Graves' disease has persisted or recurred in older patients and those with heart disease. Additionally, it is the treatment of choice for hyperthyroidism and diagnosis of thyroid dysfunction. Sodium iodide 123I is available for scanning procedures.

Radioactive iodine ablation therapy is commonly used in the treatment of hyperthyroidism and diagnosis of thyroid dysfunction. Sodium iodide 131I is available as a solution or in capsules containing essentially carrier-free 131I suitable for oral administration. Sodium iodide 123I is available for scanning procedures. Radioactive iodine treatment for hyperthyroidism is usually indicated in older patients and those with heart disease. Additionally, it is the best form of treatment when Graves’ disease has persisted or recurred after partial thyroidectomy and when prolonged treatment with anti-thyroid drugs has not led to remission. Finally, it is also indicated in patients with toxic nodular goiter, since the disease does not go into spontaneous remission. Since therapeutic outcomes are not seen right after radioactive iodine treatment, clinicians often require patients to continue with anti-thyroid drug treatment until positive results are confirmed. Hypothyroidism symptoms are usually seen within 2 to 3 months of radioactive iodine ablation therapy. If complete ablation fails 6 months after the radioactive iodine therapy, repeated treatment is recommended.

The main contraindication for the use of 131I therapy is pregnancy. Passage of TRAb through the placenta can cause fetal hypothyroidism. After the first trimester, radioactive iodine is best avoided because there may be adverse effects of radiation on fetal tissues.

Anti-thyroid drugs during pregnancy and lactation

During pregnancy, propylthiouracil is the drug of choice to manage hyperthyroidism because of its failure to traverse the placental barrier. The use of methimazole is associated with congenital anomalies and the very rare teratogenic syndrome termed “methimazole embryopathy,” which is characterized by choanal or esophageal atresia. Should propylthiouracil be unavailable, methimazole (or carbimazole) is still widely used in pregnancy. The USPSTF recommendation level of this alternative drug in pregnancy is B, evidence is fair (157).

Propylthiouracil is given during the first trimester of pregnancy. The goal of the treatment is to maintain maternal free-thyroxin serum level in the upper non-pregnant range. Keeping the maternal free-thyroxin serum level at the upper range of the non-pregnant thyroxin range provides fetal protection from possible hypothyroidism induced by anti-thyroid medication (158). Once euthyroid state has been achieved both clinically and biochemically, the dose of anti-thyroid drug should be reduced to avoid fetal hypothyroidism. If the maternal free thyroxine serum level is maintained at or slightly above the upper limit of normal, the risk of fetal hypothyroidism is clinically insignificant.

Propylthiouracil and methimazole are both considered safe in lactating women. Both appear in breast milk (methimazole more than propylthiouracil) but in minimal concentrations. Research studies of breast-fed infants have shown normal thyroid function and normal subsequent intellectual development in exposed infants.

Remission

There have been various attempts to put in place more effective therapeutic protocols for the use of anti-thyroid drugs to improve the likelihood of remission, including the alteration of the dose and length of treatment, and combining anti-thyroid medications with thyroxine therapy. Research have shown that patients with severe forms of hyperthyroidism, extensive gland enlargement, or high serum T3-T4 ratio to be less likely to proceed to remission after completing a course of drug treatment than those with milder disease and smaller goiters.

If anti-thyroid drugs have immunosuppressive effects, a higher dose or longer treatment duration may improve the likelihood of remission. Treatment with anti-thyroid drugs for 12 to 18 months is the usual practice, as recommended in a recent systematic, evidence based review (159).

Discontinuation of anti-thyroid drugs

Therapy with anti-thyroid drugs is usually tapered off after 12 to 18 months. The likelihood of relapse is increased in patients with normal serum levels of free thyroxine and triiodothyronine but suppressed serum thyrotropin levels. Relapse usually occurs within the first three to six months after the medication is stopped.

As much as 75 percent of women in remission who become pregnant will eventually develop postpartum relapse of Graves disease or thyroiditis. A lifetime monitoring of thyroid function is needed for patients in remission, since the development of spontaneous hypothyroidism can occur years after initial diagnosis and treatment. Patients need to be aware of the risk of disease. Subsequent treatment outcomes of radioactive iodine treatment may be influenced by medication with anti-thyroid drugs. For example, propylthiouracil is associated with an increased risk of treatment failure with radioactive iodine. The same effects are not seen with the use of methimazole. The radio-protective effect of propylthiouracil may stem from neutralizing effects on the iodinated free radicals produced by radiation exposure. The radioprotective effect can be easily addressed by increasing the dose of radioactive iodine (160).

Ionic Inhibitors

The term “ionic inhibitors” designates substances that interfere with the concentration of iodide by the thyroid gland. The effective agents are anions that resemble iodide; monovalent, hydrated anions of a size similar to that of iodide. The most studied example, thiocyanate, differs from the others qualitatively as it is not concentrated by the thyroid gland, but when given in large doses may inhibit the organification of iodide. Thiocyanate is produced following the enzymatic hydrolysis of certain plant glycosides (161).

Among other anions, perchlorate (ClO4) is ten times more active than thiocyanate. Perchlorate blocks the entrance of iodide into the thyroid by competitively inhibiting the NIS. Although perchlorate can be used to control hyperthyroidism, it has caused fatal aplastic anemia when given in excessive amounts (2 to 3 g daily). Over the past few years, however, perchlorate in doses of 750 mg daily has been used in the treatment of Graves disease and amiodarone-induced thyrotoxicosis (161).
Surgical intervention

Patients with thyroid disorders, in the course of treatment may be candidates for surgical management due to various reasons. One of the main reasons is ineffective pharmacological treatment and unsuccessful medical management, particularly in patients with overactive thyroid glands (hyperthyroidism). The patients with comorbidities or pregnant and requiring urgent normalization of thyroid function are often the right candidate for the surgical treatment. Thyroidectomy is rarely indicated in Graves disease in the US. Thyroid surgery is unavoidable in diagnosed thyroid cancer. Even the patient with benign thyroid nodule (goiter) may also require thyroid surgery due to the compressive symptoms (breathing and swallowing difficulties) caused by large nodules.

There are various surgical options available for patients with thyroid disorders, namely:

1. **Total thyroidectomy**: It is reserved for thyroid cancer, severe thyroid disease, multinodular goiter and substernal goiter. It carries the risk of hyperparathyroidism and laryngeal nerve damage (165) (166). In subtotal thyroidectomy, some of the thyroid tissues are preserved while reducing the incidence of hypothyroidism to 25 percent. Patients are then put on lifelong replacement therapy with thyroid hormones.

2. **Thyroid lobectomy**: It is also known as hemithyroidectomy and indicated in patients with toxic nodule or diseases involving smaller region of the thyroid gland. Surgeons also do this surgery a 2 cm incision. Its main advantage is a further reduction of incision length, minimal anatomic manipulation and better visualization. As a result, patients are able to go home after a 6 hour observation period in the recovery room. Patients who are asked to stay overnight generally have very large goiters, advanced cancer, bleeding disorders.(169).

3. **Isthmectomy**: It refers to surgical removal of the band tissue (isthmus) connecting the two lobes of the thyroid gland. A study by Perez-Ruis et al. found the feasibility and efficacy of isthmectomy in the treatment of solitary thyroid nodules confined to the isthmus (167).

4. **Completion thyroidectomy**: It refers to the surgical removal of the remaining portion of the thyroid gland. It is usually done after thyroid lobectomy when the thyroid tissues are suggestive of thyroid cancer. A study by Rafferty et al. concludes it as a safe and appropriate option in the management of select patients with well-differentiated thyroid cancer in which a definitive preoperative or intraoperative diagnosis is not available. The operation usually entails longer recovery period and thus, hospitalization (168).

Minimally invasive thyroid surgery

Minimally invasive thyroid surgery, as the name implies, is primarily defined by the reduced incision length which can be achieved by modifying the traditional surgical techniques or by the use of endoscopes.

The patients who are good candidates for this procedure are those with:

- Thyroid cancers less than 2 cm.
- Thyroid nodules less than 3.5 cm.
- Smaller goiters.
- Glands free of thyroiditis.

Minimally Invasive Video Assisted Thyroidectomy (MIVAT) is a technique where part of the surgery is done with an endoscope through a 2 cm incision. Its main advantage is a further reduction of incision length, minimal anatomic manipulation and better visualization. As a result, patients are able to go home after a 6 hour observation period in the recovery room. Patients who are asked to stay overnight generally have very large goiters, advanced cancer, bleeding disorders.(169).

Anesthesia for thyroid surgery

Generally, thyroid surgeries are done under the general anesthesia. Recent advances in thyroid surgery have enabled some surgical procedures to be performed under local anesthesia. Some of its benefits include decreased morbidity and mortality, and quick recovery (172).

Preparation of patient for surgery

Days prior to surgery, patients are evaluated for potential risk factors. Pre-operative blood investigations such as complete blood count (CBC), basic metabolic profile (BMP), coagulation profile are generally ordered. The presence of existing co-morbidities such as heart disease is evaluated using EKG and chest X-ray; this is especially important for candidates over 40 years of age.

Recovery after thyroid surgery

Generally, the postoperative recovery time in thyroid surgery is very short. The patient starts eating, drinking, and walking around 6 to 8 hours after the surgery. The patient is advised to avoid heavy work, swimming and soaking the wound while bathing to prevent wound infection. Patients may feel some postoperative symptoms such as sore throat, incision site pain, little redness, and swelling at incision site.

Five percent of patients who underwent total thyroidectomy suffered from hypocalcemia due to the sudden non-functioning parathyroid glands. These patients are usually put on postoperative calcium supplementation.

Normal recovery time is 1-2 weeks. The patient should avoid strenuous activities and return to normal lifestyle after 4 weeks.
Complications (risks) of thyroid surgery

In most of the cases, thyroid surgery is safe with few serious complications, namely (173):

- Bleeding: As with any operation, there are always chances of bleeding. The usual blood loss in thyroid surgery is very minimal, about 1 tbs only. The procedure rarely needs blood transfusion. The prevention of postoperative bleeding depends on sound intraoperative hemostasis which is achieved using a clamp and tie, surgical clips, diathermy, ultrasonic coagulating-dissection such as a harmonic scalpel (HS) or electrothermal bipolar vessel sealing systems (EBVSS). Before closing the wound, it must be irrigated well and residual bleeding contained. Finally, neck dressings are best avoided since covering the wound may mask hematoma formation, delaying its recognition. The main risk, however, is aspiration of the blood in the trachea which may very well lead to life threatening complication. Post-operative observation is required for up to 6 to 8 hours after surgery.

- Laryngeal nerve injury: The recurrent laryngeal nerve (RLN) which innervates the vocal cords passes just behind the thyroid gland bilaterally. Mechanical injury to the nerve such as complete or partial transection, traction, contusion, crush, burn, misplaced ligature, and compromised blood supply during surgery affects the cords and may result in temporary voice hoarseness which usually resolves within a few days. There have been reported cases of occasional permanent changes to voice after laryngeal nerve injury. A serious consequence of a RLN injury is true vocal-fold paresis or paralysis.

- Hypocalcemia: The 4 parathyroid glands lie behind the thyroid gland and regulate blood calcium levels. Injury or accidental removal of these glands results in hypocalcemia.

- Wound infection: Infection at the incision site is very rare (less than 1%). Postoperative infection usually manifest as superficial cellulitis or as an abscess. Additionally, erythema, warmth, and tenderness of the neck skin around the incision may be observed.

- Seroma: Seroma is a collection of fluid under the incision. In most cases, seroma resolves within a few days after surgery.

Chemotherapy

Unlike other forms of cancer, the key treatment for the majority of thyroid cancer is not chemotherapy. Chemotherapy is usually not the first line of treatment used for thyroid cancer. The reason is that better outcomes are seen with thyroid surgery in combination with radiotherapy. Chemotherapy is occasionally used in the treatment of advanced thyroid cancer or thyroid cancer that has reappeared and increased in severity after the primary treatment. Additionally, chemotherapy can be given to patients with thyroid cancer as an experimental treatment during clinical trials to chemotherapeutic drugs for various types of thyroid cancers (174).

Indications of chemotherapy for papillary and follicular carcinoma

The treatment of papillary and follicular carcinoma of the thyroid involves surgical removal of the thyroid gland followed by radioactive iodine and hormonal replacement therapy. But when metastatic disease has already been established, there are minor chances of completely curing the disease. In such cases, external radiotherapy and TSH suppression takes the lead role. If this approach also fails to stop disease progression, then chemotherapy may be considered (174).

Chemotherapy for medullary carcinoma

Medullary carcinoma is a neuroendocrine tumor of parafollicular cells of the thyroid gland that do not uptake iodine. The primary mode of treatment is extensive and meticulous surgical resection of the tumor along with the thyroid gland. There is almost no role of external-beam radiotherapy. And cells do not respond to radioactive iodine therapy or TSH suppression by hormonal therapy. So the patient of metastatic, progressive medullary carcinoma is a strong candidate for systemic and targeted chemotherapies (174).

CHEMOTHERAPY FOR ANAPLASTIC CARCINOMA

Anaplastic carcinoma is an undifferentiated tumor that shows very aggressive progression and metastasis with very poor prognosis. Most of the treatments are ineffective. Most of the time, anaplastic thyroid cancers are even resistant to external radiation therapy so occasionally, chemotherapy may be used to sensitize the anaplastic thyroid cancer cells to external-beam radiation therapy. In some cases, chemotherapy is often thought to be the first line of treatment on investigational basis (175).

Dosage and administration

The current existing guideline in the chemotherapeutic management of metastatic thyroid cancer patients is use of doxorubicin, an anthracycline antibiotic. The antitumor effects of doxorubicin stem from its RNA and DNA synthesis inhibition. However, the prognosis even with this treatment is not very hopeful. It only produces partial relief. To date, there is very little clinical data in the treatment of patients with thyroid cancer with doxorubicin. A study involving 49 patients with nonanaplastic thyroid carcinoma treated with doxorubicin monotherapy or doxorubicin combinations with cisplatin showed that only 3% of patients responded to the treatment. In contrast, another research study showed better response rates to doxorubicin, with approximately one-third of thyroid cancer patients responding; the highest and lowest responses were found in patients with medullary type and undifferentiated thyroid carcinomas, respectively (176).

Doxorubicin and cisplatin are either given separately or as combination treatment. The recommended dose of doxorubicin (monotherapy) is 60 to 75 mg/m2 given as an IV bolus. Each cycle is usually done every 3 to 4 weeks. The course of the treatment runs for at least 6 months or more, depending upon the extent of clinical responses and laboratory assessments.

Chemotherapy with cisplatin or doxorubicin has very low value in terms of response the drug produces. It is seldom helpful to the patient of thyroid cancer by producing the objective responses (generally for short durations). The nature of the chemotherapy drug is highly toxic (cisplatin or doxorubicin), chemotherapy may be considered in symptomatic patients with recurrent or progressive disease. However, chemotherapies have benefited the thyroid cancer patients with pulmonary, bone or nodal metastasis and quality of life of patients have improved, but yet unable to develop any standard protocol of the chemotherapeutic management of the thyroid cancer patients (177).
Side effects of chemotherapy treatment

Adverse effects reported from clinical trials include irreversible cardiomyopathy, cardiac arrhythmias, nausea, vomiting, granulocytopenias, infertility, and alopecia. Apart from this, both doxorubicin and cisplatin can cause sick feeling and increases the risks of infection by lowering the immune system (177).

The specific side effects of doxorubicin and cisplatin are summarized in the following table.

<table>
<thead>
<tr>
<th>Doxorubicin</th>
<th>Cisplatin</th>
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<tbody>
<tr>
<td>Ulcers in mouth</td>
<td>Ototoxicity</td>
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<tr>
<td>Red urine for about 24 hours</td>
<td>Nephrotoxicity</td>
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<tr>
<td>(as the drug excreted through</td>
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<tr>
<td>kidney)</td>
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<tr>
<td>Increased skin sensitivity to</td>
<td></td>
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<tr>
<td>sun, darkening of skin</td>
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<tr>
<td>Skin darkening is temporary and</td>
<td></td>
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<tr>
<td>disappears once the treatment is</td>
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<tr>
<td>completed</td>
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THYROID DISEASE MONITORING

Physical exam

The physical exam for the thyroid gland consists of palpation and inspection.

Techniques (178):
1. The location of the thyroid is identified by inspection.
2. Using the anterior or posterior approach, palpate the thyroid to identify nodules.
3. Note the size and number of nodules.
4. Note the consistency of the nodule.
5. Palpate regional lymph nodes for consistency and mobility.

According to Smith, the examination proceeds in the following ways (178):

1. Place the patient’s head in slight hyperextension with good cross light falling on the anterior neck and then ask the patient to swallow. The outline of the thyroid gland in thin individuals can be observed frequently as a protuberance on both sides of the trachea moving, 2 cm below the crest of the thyroid cartilage.
2. Look for abnormal enlargement, contour, asymmetry, and masses while the patient swallows repeatedly. The neck should also be inspected for abnormal masses and prominent pulsations. Note the size and number of nodules. Note the consistency of the nodule. Palpate regional lymph nodes for consistency and mobility.
3. Frequently it is advantageous to examine the gland while standing behind the patient. Identify the thyroid cartilage, the thyrotrigoid membrane, and the cricoid cartilage, a horizontal structure 5 mm wide that marks the superior border of the isthmus. Palpate the isthmus (frequently impalpable unless enlarged), and if standing to the side of the patient, slide the tips of fingers so that their palmar surfaces rest on the trachea with the dorsal surface medial to the sternocleidomastoid muscle. This ipsilateral lobe can be palpated simultaneously with the thumb or with the other hand from the opposite direction.
4. When standing behind the patient, identify the landmarks and isthmus with one hand, and when in position to feel the thyroid lobe on that side, place the fingers of the other hand symmetrically on the other side of the trachea. Again, identify each lobe while the patient swallows. Feel the gland’s surface, note any asymmetry, texture, and estimate the size of each lobe (normally 7 to 10 g). When goiter is present, measure any discrete masses as well as the neck’s greatest circumference. A penciled tracing of the goiter’s outline provides a reliable record for future comparison. One should also palpate the neck for lymphadenopathy.

Combining the physical examination of the thyroid gland with proper evaluation of associated signs and symptoms is the best way to monitor disease process. There is no direct correlation between size and function. A person with a goiter can be euthyroid, hypothyroid or hyperthyroid. Monitoring the response to therapy directed at decreasing the size of the thyroid in cases of symptomatic goiter (179).

In addition of the thyroid gland itself, the physical examination should include signs of abnormal thyroid function and extra-thyroidal features such as ophthalmopathy and dermopathy. In Graves’ disease, monitor lid retraction, periorbital edema and proptosis (179).

Assessment of the enlarged nodule and multiple nodules are required in diffuse non-toxic goiter and non-toxic multinodular goiter, respectively.

Other aspects of the clinical examination for thyroid disease include (179):

- **Reflexes**: The area near the Achilles tendon is struck with a small mallet to test the reflex. Hyper-responsiveness may point to hyperthyroidism, and slow reflexes may indicate hypothyroidism.

- **Cardiovascular integrity**: Bradycardia may point to hypothyroidism, and tachycardia may indicate hyperthyroidism. Other patients with hyperthyroidism may also have hypertension and arrhythmias such as atrial fibrillation.

- **Weight monitoring**: Rapid and unexplained weight gain can point to hyperthyroidism, and rapid unexplained weight loss may be a sign of hyperthyroidism.

- **Basal body temperature**: Low body temperature is encountered in some patients with underactive thyroid gland.

Evidence rating: Hair loss along the outer edge of the eyebrows, and puffiness or swelling of the eyelids or face are other common symptoms of hypothyroidism.

**Examination of the eyes**: The eyes are commonly affected by thyroid disease. The ocular symptoms are (179):
- Bulging or protrusion of the eyes
- Stare in the eyes
- Retraction of upper eyelids
- A wide-eyed look
- Infrequent blinking
- Lid lag

Quantity and quality of hair: Significant hair loss is observed in both hyperthyroidism and hypothyroidism. Coarse, brittle or straw-like hair can point to hypothyroidism. Thinning, finer hair may point to hyperthyroidism (179).

Examination of cutaneous features: Hyperthyroidism manifests itself in different skin-related signs such as yellowish, jaundiced complexion, unusually smooth, young-looking skin, blisters around the face, hives, and lesions or patches of rough skin on the shins (pretibial myxedema) (179).

Hyperthyroidism also shows signs on the nails and hands such as (179):
- Onycholysis: separation of the nail from the underlying nail bed, also called Plummer’s nails
- Swollen fingertips, also called acropachy

- Swollen fingertips, also called acropachy
- Onycholysis: separation of the nail from the underlying nail bed, also called Plummer’s nails
- Swollen fingertips, also called acropachy
Review of other clinical signs

<table>
<thead>
<tr>
<th>Evaluation and assessment of other clinical signs of hyperthyroidism include (179):</th>
</tr>
</thead>
<tbody>
<tr>
<td>● Tremors</td>
</tr>
<tr>
<td>● Shaky hands</td>
</tr>
<tr>
<td>● Hyperkinetic movements -- table drumming, tapping feet, jerky movements</td>
</tr>
<tr>
<td>Evaluation and assessment of other clinical signs of hypothyroidism include:</td>
</tr>
<tr>
<td>● A dull facial expression</td>
</tr>
<tr>
<td>● Slow movement</td>
</tr>
<tr>
<td>● Slow speech</td>
</tr>
<tr>
<td>● Hoarseness of voice</td>
</tr>
<tr>
<td>● Edema (swelling) of the hands and/or feet</td>
</tr>
</tbody>
</table>

TSH

Since thyroid disorders have diverse clinical manifestations, clinicians need to stay vigilant for subtle and nonspecific signs and symptoms. To aid in this endeavor, frequent laboratory investigations are part of the essential tools to monitor therapy and disease progression.

TSH screening test is used not just in the diagnosis but also monitoring ongoing therapy for thyroid disorders. It is the most reliable screening test for monitoring ongoing therapy for hypothyroidism and hyperthyroidism. The higher the level of TSH, the higher the amount of T4 and T3 released into the blood (180).

Response to L-thyroxine (levothyroxine sodium) is best monitored biochemically beginning at least 6 weeks after starting therapy. Thyroid function should be assessed every 6-8 weeks until the patient is euthyroid and then rechecked annually, aiming to maintain T4 and TSH within the normal range. However, serum thyroid hormone levels normalize before serum TSH. Serum thyroid hormone concentrations increase first, then the TSH secretion falls because of the negative feedback action of levothyroxine on the pituitary and hypothalamus.

Patients who are not known to have a disturbance of hypothalamic-pituitary function and have been on thyroid replacement therapy for longer than three months with TSH test performed in the previous year have:
1. TSH that is usually the sole initial test of thyroid function
2. TSH result within the reference range

People who have been treated for thyroid cancer benefit from having a suppressed TSH, because TSH is thought to promote tumor recurrence.

High T4 with suppressed TSH levels suggests overtreatment. Suppression of TSH with serum T4 at the upper end of the normal range or even slightly elevated is sometimes observed in those receiving recommended doses. These laboratory findings indicate overtreatment and dose reduction since there is evidence of long-term cardiovascular risk linked to mild overtreatment (180).

Undertreatment occurs more often than overtreatment. With evidence suggesting that up to 25 percent of patients receiving L-thyroxine for hypothyroidism being under-treated, yearly measurements of serum TSH may be valuable in assessing the adequacy of therapy and compliance. Patients who do not adhere to the recommended therapy and take L-thyroxine a few days before a clinic visit will have normal or even elevated T4 levels with paradoxically raised TSH (180).

Patients with symptoms such as unrelenting tiredness, somnolence, or slight cognitive problems like forgetfulness may have their doses increased by 25 μg daily or on alternate days.

If the initial diagnosis of hypothyroidism is still in question once L-thyroxine treatment has been started, the clinician may opt to stop treatment for 6 weeks and measuring serum TSH and T4 in the untreated patient.

In most patients, dose adjustments for L-thyroxine are often not required, with pregnancy being an exception. In the latter, dose increments are required in order to maintain serum TSH levels. Therapy with some drugs such as rifampicin, phenytoin, carbamazepine (increased clearance of thyroxine) and cholestyramine, sucralfate, aluminium hydroxide, ferrous sulphate (reduced absorption of thyroxine) also alters L-thyroxine dose requirements because of their effects on its absorption or metabolism.

Generally, TSH suppression is not a desirable outcome because of its potential adverse effects on cardiac function like cardiac hypertrophy, atrial fibrillation and bone metabolism (180).

fT3 and fT4

Measuring fT4 and fT3 is helpful in checking the immediate response to therapy before the TSH has had a chance to respond. The TSH typically takes six to eight weeks to accurately reflect thyroid hormone status after therapy. A common scenario is following treatment of hyperthyroidism; an appropriate response to therapy is seen when the fT4 and fT3 levels return to normal, even with an existing TSH suppression.

Additionally, the TSH test helps clinician to fine-tune therapy to suit individual patients’ needs once the fT4 and total T3 levels are in the normal range (180). An example is when a patient with TSH of 2.5 on 100 mg dose of L-thyroxine still experiences symptoms (e.g. increased cold sensitivity and fatigue). In this case, the clinician may attempt to increase the dose to 112 mg daily to achieve a TSH close to 1.0, after which reassessment of symptoms is required after six weeks. If symptomatic control has been achieved and TSH tests corroborate the clinical finding, the existing dose needs to be maintained. On the other hand, if no improvement is seen despite a TSH level in the low-normal range, the dose needs to be reduced back to 100 mg since the symptoms are most probably not related to thyroid function.

Older individuals need lower doses of L-thyroxine. Specifically, they may require less than 1.0 μg/kg/day to be titrated slowly. Usually, a 25 μg starting dose is recommended for patients with diagnosed ischemia followed by increments of 25 μg every three to four weeks until the full replacement dose is attained. Some studies point that a higher target TSH (0.5-3.0 mIU/L) value may actually be of more beneficial value to older patients (181).

In cases of severe hypothyroidism, the administration of L-thyroxine loading dose is the quickest way to achieve therapeutic fT4 level because the excess of unoccupied binding sites may blunt the fT4 response to treatment.

As mentioned before, dose requirements for L-thyroxine increase during pregnancy. Thyroid function should be monitored closely, with TSH and fT4 tests obtained every trimester of the pregnancy. L-thyroxine dose should be increased (usually by 50 μg/day) to maintain a serum TSH between 0.5 and 2.0 mIU/L and a serum fT4 in the upper third of the normal reference interval (181).

Certain agents are known to impair the absorption of L-thyroxine from the gut; patients on thyroxine therapy should be advised to take their thyroxine at least 4 hours apart from these medications. Patients starting chronic therapy with cholestyramine, ferrous sulfate, calcium carbonate, soy protein, sucralfate and antacids containing aluminum hydroxide
that interfere with L-thyroxine absorption may require a higher dose to keep TSH within the therapeutic target range. Additionally, patients on rifampin and anticonvulsants may also need dose increments to maintain the TSH within the therapeutic target range because these agents also interfere with the drug’s metabolism (181).

Close monitoring of patients being treated for Graves disease or other causes of hyperthyroidism requires at least a three-month interval after the start of therapy before a repeat measurement of TSH level is performed because of the prolonged suppression of pituitary TSH secretion. If a biochemical measurement of thyroid status is required during this time period, fT4 is preferred (181). Similarly, when pituitary or hypothalamic disease is suspected, fT4 measurement is preferred to assess the adequacy of thyroid replacement therapy. Consultation with the lab physician is recommended when the test result is in conflict with the clinical presentation.

**Monitoring change and progress**

It is important to review the action plan against the timeline at regular intervals with the team. It may be helpful to discuss the following questions:

1. Is the process working?
2. Are the goals for improvement being achieved?
3. Are the goals still appropriate?
4. Do we need to develop new tools to achieve the goals?

**Radioactive iodine ablation**

Ablation of the gland happens during 2-5 months following radioactive iodine therapy, at which time, many patients become hypothyroid. Checking thyroid functions every 4-6 weeks until the patient has stable thyroid functions is recommended.

After stable thyroid functions have been established, a partial or low-dose thyroid hormone replacement is recommended (50-75 µg/day, adjusted every 6-8 weeks to normalize the TSH level). Several weeks after a subtotal thyroidectomy for hyperthyroidism and discontinuation of anti-thyroid therapy, many patients develop hypothyroidism, depending on how much functional thyroid tissue is left by the surgeon. A partial hormonal replacement therapy with L-thyroxine is recommended immediately after surgery, usually at doses 50-75 µg/day. Postoperative thyroid function tests should be taken after 4-8 weeks, and the L-thyroxine dose adjusted according to TSH levels (181).

**Thyroid surgery**

Routine check ups following thyroid surgery may be needed because of the possible development of hypothyroidism (from chronic thyroiditis), recurrent hyperthyroidism, or eye disorders at some point in the future. The majority of patients remain euthyroid after a lobectomy or lobectomy plus isthmusectomy to treat a toxic adenoma or toxic multinodular goiter with a dominant nodule. To make sure that normal thyroid function has been firmly re-established, thyroid function tests should be obtained 3-4 weeks after a lobectomy.

**COMORBIDITIES AND CONCOMITANT THERAPY**

**Comorbidities**

Comorbidities adversely affect patients with compromised thyroid function in several ways, namely:

- Response to therapy
- Proper evaluation of associated illness
- Overall prognosis

**Autoimmune thyroid disease and comorbidities**

The two main thyroid diseases with autoimmune etiology are Graves disease and Hashimoto’s thyroiditis. Studies have indicated that approximately 25 percent of the people with Hashimoto’s thyroiditis also have other autoimmune diseases.

**Diabetes mellitus**

Approximately 10 percent of patients with diagnosed type 1 diabetes mellitus ultimately develop chronic thyroiditis in their lifetime, which may include the insidious onset of subclinical hypothyroidism. Patients with diabetes should be examined for the possibility of goiter. Patients with one organ-specific autoimmune disease (e.g. thyroid disease) are at greater risk of developing other autoimmune disorders; it is not uncommon that 30% of women with diagnosed type 1 diabetes also have a coexisting thyroid disease. A number of studies have found that a higher than normal prevalence of hypothyroidism in type 2 diabetic patients (182).

Thyroid dysfunction adversely affects diabetes control. Hyperthyroidism is mainly linked to poor glycemic control and elevated insulin requirements. Additionally, overstimulation of hepatic gluconeogenesis, fast glucose absorption in the GIT, and even increased insulin resistance may be observed. Moreover, thyroid overactivity may unmask latent diabetes (182). In clinical practice, the existence of hyperthyroidism and diabetes has several implications, namely (182):

- Cautious diagnosis of glucose intolerance needs to be kept in mind since elevated blood sugar level may improve with treatment of thyrotoxicosis.
- Hyperthyroidism should be considered in diabetic patients with unexplained high blood sugar levels.
- Anticipate worsening of glycemic control in diabetic patients with hyperthyroidism and adjust treatment accordingly. Recovery to euthyroid state will subsequently result in better glycemic control.

In hypothyroidism, the decreased rate of the breakdown of insulin may also reduce the insulin dose requirement. The presence of hypoglycemia is uncommon in isolated thyroid hormone deficiency and should be suspected of diminished pituitary function in a patient with underactive thyroid function. Moreover, hypothyroidism usually coexists with various abnormalities in plasma lipid metabolism,
Ayurvedic therapy is based on the doctrine that certain substances given to address such symptoms. The beta blocker, propranolol, has and sensitivity to heat. Adrenergic blockers, or beta blockers, are from over-expression of beta-adrenergic receptors and beta-receptor hyperthyroidism are caused by adrenergic overstimulation resulting hyperthyroidism. Many of the clinical manifestations of are adrenergic symptoms to be addressed such as in overt Another exception to monotherapy is in cases where there study to fully explore the potential of this combination (189). anaplastic thyroid cancer. The promising results warrant a phase 2 use of docetaxel with radiation is highly effective in the treatment of necessary to achieve favourable prognosis. For example, concomitant use of docetaxel with radiation is highly effective in the treatment of anaplastic thyroid cancer. The promising results warrant a phase 2 study to fully explore the potential of this combination (189). Another exception to monotherapy is in cases where there are adrenergic symptoms to be addressed such as in overt hyperthyroidism. Many of the clinical manifestations of hyperthyroidism are caused by adrenergic overstimulation resulting from over-expression of beta-adrenergic receptors and beta-receptor stimulation. These symptoms include palpitations, anxiety, tremors, and sensitivity to heat. Adrenergic blockers, or beta blockers, are given to address such symptoms. The beta blocker, propranolol, has become the drug of choice because most of these effects are mediated by beta-receptors. Furthermore, it has fewer associated adverse effects. Some reports suggest that propranolol decreases T3 plasma levels by blocking the peripheral deiodination of T4. Initial doses of 20–40 mg of propranolol four times daily are typically effective to maintain the heart rate below 100 beats/min. Young patients and those with more severe symptoms may require higher doses. Contraindications to beta-blockers are congestive heart failure, cardiomyopathy, sinus bradycardia, asthma, and COPD. Other drugs such as reserpine and guanethidine, both depletors of catecholamines, clonidine, and calcium channel blockers decrease the adrenergic symptoms of thyrotoxicosis. Calcium channel blockers such as diltiazem and verapamil are used especially when there is contraindication to beta-blockers. Diltiazem 120 mg every eight hours is effective to reduce the heart rate.

**ALTERNATIVE THERAPY**

**Ayurveda**

Ayurvedic therapy is based on the doctrine that certain substances from vegetable, animal and mineral origins have curative values. The fundamental principle of ayurveda is that all diseases in the body originate from the imbalance of “vatta”, “pitta” and “kapha”.

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According to Ayurvedic principles, there are many herbs that can help in thyroid disease. “Kanchanara Guggulu” is the most potent herbal formula listed in the Indian pharmacopoeia for treating all types of thyroid disorders. It is known to remove dormant “kapha” from the body. It also removes toxins from the lymphatic system.

Other Ayurvedic herbs like Triphala, Shilajit, Punarnava, Gokshura and Brahmi are combined in many ways to treat thyroid disorders. In case of hyperthyroidism, the herb Kaishore Guggulu is used to reduce “pitta”. Emphasis is also given on herbs that contain iodine and those that promote thyroid function and boost immunity (190).

**Homeopathy**

Homeopathy is a system of drug therapeutics based on the “law of similar”. For example, a drug or substance that causes the symptoms of a disease in healthy people will cure similar symptoms in sick people provided that it is homeopathically potentized. Homeopathy offers a holistic approach; instead of focusing on the thyroid disease, it considers the patient as a “person” which includes taking into consideration the overall personality before prescribing a medicine.

Homeopathy uses only natural substances and natural processes to prepare its remedies. There are more than fifty homeopathic remedies for thyroid disorders. The reason for multiple remedies is the fact that selection of homeopathic remedies is based on the personality and constitution of an individual. Homeopathic medications reportedly have no side effects and can be taken with multiple medications (191).

**Traditional Chinese medicine and acupuncture**

Chinese medicine believes that hyperthyroidism is the result of a yin deficiency and hypothyroidism results from a yang deficiency. There are many herbs deemed useful in treating hypothyroidism and hyperthyroidism; some of the more common ones are rou gui and fu zi, and sheng di huang, Shan Yao, and Shan Zhu Yu, respectively (192).

Chinese medicine also advocates the use of sea foods like oyster shells, Laminaria, and Sargassum in iodine deficiency goiter. Various herbs like pinellia, fritillaria, sinapis, Dioscorea bulbifera, and various types of citrus plants are useful to dissolve the thyroid mass. Concept of herbal use involves identification of the triggers that led to thyroid dysfunction. The Chinese theory emphasizes blockage of vital energy. Chinese medicine has concomitant therapies like acupuncture that support herbal treatment (192).

**Naturopathy**

Naturopathy focuses on the healing powers within the body itself. Its principles revolve around the idea that every human being has healing powers; the immune system is an integral part of it which maintains equilibrium. Naturopathy believes that disease results from a hectic lifestyle and poor eating habits that result in elevated stress levels that create unevenness and disorders within the body that in turn, affects its vital energy supply (193).

Treatment for thyroid disorders consists of natural therapies such as dietary modifications, lifestyle modifications, herbal supplements, minerals and vitamin supplements, acupuncture, hydrotherapy and massage in order to treat the underlying cause of the problem and re-establish the balance of the endocrine system, thereby, improving thyroid functions (193).

**NEW ADVANCEMENTS**

**Diagnostic techniques**

Ultrasound guided fine-needle biopsy US-FNAB

The use of fine-needle aspiration biopsy (FNAB) is the conventional method of detecting cancerous cells in thyroid nodules, but it comes with pitfalls, namely; it lacks adequate sensitivity and specificity.

When FNAB is performed under ultrasound guidance, it is capable of obtaining aspirate sample from the highest-yield portion of the nodule, thereby, reducing the chances of indeterminate results due to lack of thyroid cell sample. Needle biopsy produces indeterminate results in 75 percent of cases, with the other 25 percent classified as suspicious of carcinoma. About one-quarter of suspicious results are eventually diagnosed as thyroid cancer (194).

Multi-level molecular profiling

Endocrine experts from the University of California - Los Angeles have introduced new advancements to molecular profiling. Their techniques using genetic markers for evaluating biopsy samples with suspicious cytologic features have revolutionized the provision of optional patient care in patients with thyroid nodules, namely; by avoiding unnecessary surgery, eliminating errors, and enabling appropriate immediate and straightforward cancer treatment once suspected samples are confirmed positive for malignancy (194).

Molecular profiling proceeds in two levels:

**Level 1**: Determination of the nodule – whether it is benign or malignant

**Level 2**: Assessment of the suspicious results and refinement of procedure

There are several advantages to the multilevel approach of this technique, namely:

**Level 1**: Surgery and its associated risks, costs and inconvenience can be avoided altogether in suspicious results

**Level 2**: Complete thyroid removal and lymph node dissection are only indicated once the results are positive for all genetic markers of malignancy

A study by Ferraz et al. in Germany strongly indicates that preoperative FNAB testing for somatic mutations led to an improvement of sensitivity/specificity for indeterminate/follicular proliferation FNAB samples (195).
New treatment modalities in thyroid carcinoma

The results of a research led by Kapiteijn et al. of various published studies on novel treatment approaches in thyroid carcinoma are in PubMed, Cochrane Library, Medline and EMBASE database and abstracts are outlined below (196).

Monotarget kinase inhibitors

Gefitinib is an oral epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI). EGFR is highly expressed in malignant thyroid tissue and its genetic mutations have been associated with thyroid cancer. Furthermore, EGFR contributes to RET activation, signalling and growth stimulation. It is linked with poor prognosis in differentiated thyroid carcinoma (197).

AZD6244 is a potent, selective non-competitive inhibitor of MEK1/2 that has undergone phase 1 clinical trials with activity in two advanced thyroid cancer patients with stable disease for at least 5 months (198).

Multikinase inhibitors

The first agent is axitinib which effectively inhibits all of the VEGFRs. One of five patients with thyroid carcinoma included in the first phase of clinical trial exhibited tumor shrinkage. The second stage of the clinical II trial showed the efficacy of axitinib in any type of metastatic thyroid carcinoma, with partial remission in 30 percent of the patients (199).

The second agent is motesanib which targets the VEGFR 1–3, RET and c-KIT. During the first stage of its clinical trial, a 50 percent overall response rate was seen in patients with advanced thyroid carcinoma. Based on these promising results, a multicenter second stage clinical trial was started to test its efficacy in patients with progressive differentiated thyroid carcinoma and progressive or symptomatic medullary thyroid carcinoma (200).

The third agent is vandetanib which targets VEGFR 2 and 3, RET and EGFR. Vandetanib effectively inhibits RET/PTC3 chromosomal translocations found in some PTC and M918T RET mutations occurring in MEN2B-associated and certain medullary thyroid carcinoma. Currently, it is in the second stage of clinical trial, its efficacy being studied in patients with metastatic hereditary forms of medullary thyroid carcinoma (201).

The fourth agent is sorafenib which targets BRAF, VEGFR 1 and 2 and RET, conducting proapoptotic and antiangiogenic actions. During its second stage of clinical trial, researchers found a partial remission rate of 23 percent and a stable disease rate of 53% in mainly patients with advanced differentiated thyroid carcinoma (202).

The last agent is sunitinib which targets VEGFR 1–3, RET and RET/PTC subtypes 1 and 3. A response rate of 8 percent in differentiated thyroid carcinoma patients and 13 percent in medullary thyroid carcinoma patients was reported during a phase II trial to determine the effect of sunitinib in refractory advanced thyroid carcinoma. Furthermore, 67 percent of differentiated thyroid carcinoma patients and 87 percent of medullary thyroid carcinoma patients showed disease stabilization (203).

Latest recommendations on the radiation safety after treatment with radioiodine I-131 by the American Thyroid Association (ATA), 2011

The task force created by the American Thyroid Association to develop radiation safety recommendations for the information and guidance of medical professionals, patients and family members. The recommendations, which are compliant with the Nuclear Regulatory Commission regulations and consistent with guidelines promulgated by the National Council on Radiation Protection and Measurement (NCRP-155), can help physicians and their patients keep radiation safety post-treatment with I-131. Both clinicians and patients need to be informed of these guidelines in order to attain optimal safety.

In 2011, stricter precautions were set in order to limit the radiation exposure to family members, fetuses, children, caregivers and the general public from patients recently treated with radioiodine. The summary of the revised recommendations are discussed in detail below (224):

Radiation safety officer: All treatments should be provided by a clinician trained in the administration of radiopharmaceuticals, under safety precautions/protocols determined by the radiation safety officer. The radiation safety officer should also develop patient-specific precautions, taking into account the predicted retained radioactivity in each patient.

Pregnancy/reproduction: Women from the age of menopause to 2 years after menopause should be tested for pregnancy, and should be informed that pregnancy is a contraindication to I131 therapy. Women should avoid becoming pregnant for 6 months after treatment to allow for the normalization of thyroid levels. Men should be advised that fathering a child within 3 months of radiation exposure has not been associated with an increase in congenital abnormalities or fetal demise. They should be advised, however, that full fertility may not return for 1 year, and that they should not attempt to produce a pregnancy until at least 3 months after the completion of I131 therapy.

Breastfeeding: Breastfeeding should be discontinued because of the risk to the infant related to exposure during lactation.

Dose rate calculations to determine distance: When exposure from a treated patient at 1 meter (3.2 feet) exceeds the NRC-defined regulatory limit of less than 7 millirem/hour, people should remain at least 6 feet (1.8 meter) away, although adults can be within 1 meter of the patient for brief periods, “preferably only for minutes.” Patients should drive alone or, when riding in a car, stay as far away from other occupants as possible.

Travel through ports of entry: For 4 months after therapy, patients crossing borders (via airports, tunnels, or bridges) should carry a form specifying the date of treatment, radionuclide used, and provider contact information.

Post-treatment accommodations: Patients should not stay in hotels, should avoid public transportation, and should avoid being in close proximity to others.
Personal hygiene: Patients should use special precautions, especially during the first 48 hours, to minimize the possibility of exposing others to urine, stool, saliva, blood or bodily fluids, perspiration, or vomit.

Specialized leak-proof waste disposal bags should be made available to the patient during the restricted period.

PATIENT EDUCATION

Patient education is very important, but at times, a difficult matter to address. Many clinicians believe that patient education is an indivisible part of the management of any disease.

Patient education results in better treatment compliance and more successful treatment outcomes. But many doctors find it difficult too. It is equal responsibility of the other health care practitioners such as nurses, physician’s assistants, and pharmacists to educate patients and answer their questions whenever the situation calls for it or the need arises.

Generally, the patient should be educated thoroughly regarding the following points:

1. **The basic information about thyroid disease**
   The patient should be informed about the diagnosis. After experiencing the abnormal symptoms, the patient will appreciate basic information about the disease. Knowledge is power and for some patients, it is also a relief to finally know the cause of their suffering. The use of patient-friendly language and lesser medical jargon makes way for better patient understanding and faster communication.

2. **Nature of the disease**
   The patient should be educated regarding the nature of their disease. They need to understand the nature of their symptoms and how they can best manage it. Additionally, they should be informed about their chances of recovery (prognosis).

3. **Duration and type of treatment**
   Since most thyroid dysfunctions are chronic in nature, they need to understand that treatment and management are long term and requires regular follow up. This is very important because patient adherence is often difficult in the long run. Many patients stop their medication and follow up check ups after a few months of treatment because of the initial relief of the symptoms. Abrupt cessation of therapy has deleterious consequences; many patients who experienced relapse ended up with a more severe form of the disease that is difficult to control and stabilize.

   Additionally, hormone replacement is a key part of therapy for many hypothyroid conditions; patients need to know in advance the side effects to expect from the synthetic hormones.

4. **Dietary advice**
   Nutrition plays an important role in maintaining healthy thyroid function. Following a healthy and balanced diet is a good step towards the right direction. It helps avoid unwanted weight gain, metabolic imbalance and musculoskeletal symptoms. Research is in favor of food intake which improves thyroid function and restores metabolism. A diet rich in organic food, citrus foods, sea foods, and the so called “good” oils such as extra virgin olive oil helps improve thyroid functions. Ideally, fruits and vegetables such as carrots, spinach, olive oil, avocados, asparagus, whole-grain cereals, bananas and oily fishes should also be included.

   The patient with hyperthyroidism should avoid stimulants like caffeine and also food with natural goitrogenic properties such as cabbage, broccoli, sweet potatoes, lima beans and soy products. These foods interfere with iodine uptake and disrupt thyroid function.

   The patient with hypothyroidism who is currently on thyroid hormone replacement therapy should be advised to take the hormonail pill on an empty stomach. Additionally, they should be advised to regulate their intake of dietary fibers as they impair the absorption of synthetic thyroid hormones. There are some foods, medications and supplements which exert a similar type of effect on the gastrointestinal system and should likewise be avoided by the patient.

   Patients on hormone replacement therapy should avoid taking their thyroid hormone at the same time as:
   - Walnuts
   - Soybean flour
   - Meal containing cottonseeds
   - Iron supplements or multivitamins containing iron
   - Supplements of certain minerals like calcium, iron or multivitamins containing iron
   - Aluminium or magnesium containing antacids
   - Medications like sucralfate (used for the treatment of ulcer)
   - Some anti cholesterol drugs like cholestyramine and colestipol

   To avoid unwanted interactions with these medications, patients should eat or take them several hours before or after taking the prescribed synthetic hormone.

5. **Vitamin and mineral supplementation**
   It is medically advised that every patient with hyperthyroidism should be supplemented with multivitamins as to overcome the extra demand of the body especially vitamin A and C as well as riboflavin, thiamine, B6 and B12. A number of studies have found that up to 30% of people with advanced thyroid disease experience a vitamin B12 deficiency. As a result, patients should try to incorporate food sources rich in vitamin B12 such as mollusks, sardines, salmon, organ meats such as liver, muscle meat, and dairy. Untreated vitamin B12 deficiency can lead to irreversible damage, which is why it’s imperative for clinicians to recommend patients with thyroid disease to have their levels tested.

   Patients with hypothyroidism can also benefit from selenium and zinc supplementation. Following thyroidectomy, patient should be advised to take calcium supplementation without fail.

   **Selenium-rich foods**
   Selenium is an element which plays a role in the hormonal balance of thyroid hormones. Foods such as mushrooms, garlic, onions, eggs, beef liver, shellfish, wheat germ, sunflower seeds, and sesame seeds are rich in selenium. Regular intake of these foods may prevent thyroid dysfunctions.

   **Iodine**
   Patient should be educated regarding the role of iodine in the maintenance of thyroid functions. They should be informed that the body does not produce endogenous iodine which is why it is important to include them in the diet and that the main source depends on dietary or supplementary intake.

   **Vitamin D**
   A study by Tamer et al. have found an association between vitamin D deficiency and Hashimoto’s thyroiditis, with more than 90 percent of the study patients being deficient. However, the causal relationship, if any exists, between the two remains unclear.

   Hyperthyroidism, specifically Graves disease, causes bone density loss which can be aggravated by vitamin D deficiency. Bone mass may be recovered with subsequent therapy for hyperthyroidism with sufficient intake or adequate supplementation of bone-building nutrients, such as vitamin D, which are important during and after treatment.
Recommended foods for vitamin D intake are fatty fish, milk, dairy, eggs, and mushrooms. Patients with vitamin D deficiency may need supplemental vitamin D3 (206).

6. **Exercise**

Studies have proven that following a regular exercise plan or regular sports activity compliments medical therapy in thyroid patients. The exercise is a “natural antidote” to the symptoms of thyroid disorders like weight gain, muscle loss, low energy, depression, and mood swings.

Patients with hypothyroidism can benefit from regular exercise. It improves metabolism and replaces fat with lean muscle mass. On the other hand, patients with hyperthyroidism often suffer from sleeplessness, low energy level and mood swings which are all minimized by regular exercise.

A study by Cutovic et al. found that a structured exercise regimen exhibited dramatic improvements in fatigue levels, with more patients being able to successfully stop taking anti-thyroid medications without a relapse (208).

**PREVENTIVE AND SCREENING MEASURES**

Presently, there are no distinct recommended preventive measures against hyperthyroidism, hypothyroidism, and thyroid cancers in healthy individuals. Iodine deficiency, the leading cause of hypothyroidism outside the US, is uncommon in the country and as a result, there is no clearly defined measure to prevent the incidence of nodular goiter. Moreover, the leading cause of hypothyroidism in the US is Hashimoto’s thyroiditis, an autoimmune disease with poorly understood pathophysiology. Generally, it is not recommended that healthy individuals take extra iodine. There are however, supplemental doses of iodine in adult multiple vitamins which help healthy individuals meet their recommended daily allowance of iodine (210).

Radiation exposure (e.g. radiotherapy) is known to induce both benign and malignant thyroid nodules. Healthy individuals are advised to (211):

- Steer clear of unnecessary CT scans of the head and neck areas
- Employ thyroid shield when dental X-rays are obtained
- Avoid excessive radiation exposure

The medical opinion on screening for thyroid disease in adults is conflicted. The U.S. Preventive Services Task Force (USPSTF) has found insufficient evidence to recommend for or against routine screening for thyroid disease in adults. It acknowledges the TSH test’s usefulness in detecting subclinical thyroid disease in adults but has not found strong evidence that such screen-detected thyroid conditions have clinically improved outcomes (212). On the other hand, the American Thyroid Association (ATA) recommends thyroid function monitoring in adults at and over the age of 35 years, with follow up check ups every 5 years thereafter. Furthermore, it acknowledges that more frequent screening may be needed in individuals with risk factors or symptoms of thyroid disease (213). The Canadian Task Force on the Periodic Health Examination (CTFPHE) recommends keeping a high index of clinical suspicion for vague symptoms consistent with hypothyroidism in perimenopausal and postmenopausal women (214). The American College of Physicians (ACP) recommends monitoring women over 50 years old with one or more general symptoms that may be caused by thyroid dysfunctions (215). The American Association of Clinical Endocrinologists (AACE) recommends monitoring TSH levels women of childbearing age before pregnancy or during the first trimester (216). The American College of Obstetricians and Gynecologists (ACOG) recommends physician awareness of the symptoms and risk factors for postpartum thyroid dysfunction and evaluation of patients whenever necessary (217). The American Academy of Family Physicians (AAFP) do not recommend routine thyroid screening in asymptomatic patients below 60 years old (218).

In the US, there are three types of thyroid disease preventive measures, namely (219):

1. **Primary prevention** is the prevention of onset of new disease in previously undiagnosed individuals. These measures typically involve public health actions as promotion of healthy diet and lifestyle. In the case of thyroid disease prevention especially, the most important measure is to ensure and secure sufficient iodine intake in iodine-deficient areas.

2. **Secondary prevention** involves the termination or delay of disease progression thyroid diseases. A good example of secondary prevention is the screening of individuals with subclinical hypothyroidism. If detected, another form of secondary prevention is warranted in the form of treatment with thyroxine to prevent further thyroid failure.

3. **Tertiary prevention** refers to the avoidance of disease progression. It entails frequent and regular clinical and laboratory assessments. A good example is the prevention of thyroid hormone overdose.

**CONCLUSION**

There is a considerably high prevalence of thyroid diseases among the American population, with approximately 20 million having one form or another. The American Thyroid Association estimates that sixty percent of this number are unaware of their condition, the majority of which are women, especially elderly ones. The most diagnosed forms are of autoimmune origins, Graves disease and Hashimoto’s thyroiditis. Thyroid cancers and iodine-deficiency goiters are rare.

Despite the prevalence and healthcare costs associated with their complications, adult-based population screening measures have been recommended, but general consensus as to the exact guidelines remain elusive with various health and federal organizations undecided and conflicted on the issue.

Thyroid diseases generally present a positive clinical outlook once therapy is established and maintained. The exception to this is thyroid cancer, with anaplastic carcinoma offering the poorest prognosis. Thyroid diseases mostly present with general and nonspecific symptoms, resulting in delayed diagnosis. Hypothyroidism is commonly addressed with hormone replacement therapy with the drug L-thyroxine, while hyperthyroidism is usually treated with the anti-thyroid drugs, propylthiouracil and methimazole. Propylthiouracil is the drug of choice in pregnant women. Thyroid disorders during pregnancy pose serious risks to both the mother and the baby, thus, requiring immediate management and careful monitoring throughout the gestational period and after delivery.
Severe and unremitting forms of thyroid diseases are addressed with radioactive iodine therapy and thyroidectomy. Radioactive iodine therapy makes use of ionizing radiation which presents a risk of unnecessary post-treatment exposure to individuals who come in contact with those who recently received it. Recent advances have made thyroidectomy a straightforward operation, requiring minimal incision and reduced recovery period. It has minimal risks. Furthermore, adjunct therapy to address symptomatic complaints associated with thyroid dysfunction is widely used in conjunction with the standard treatments. The diagnosis of thyroid diseases, especially those with suspected and non-determinable FNAB samples have been further advanced with the help of ultrasound technology. Thyroid function tests have been and still are the primary tests to determine the functional status of the thyroid gland. Despite its several pitfalls, TSH screening test remains the gold standard in the initial evaluation of the root cause of the thyroidal symptoms. The popularity of alternative therapy in the treatment process has made patient education an indispensable part of patient-clinician relationships. Ideally, patients need to be aware of their diagnosis, the treatment required and their role in it, especially adherence to the prescribed therapy. The likelihood of relapse due to abrupt discontinuation of therapy is increased in patients who are not aware of the consequences of such actions.

Last but not the least, a number of studies has shown various risk factors to thyroid diseases. Although not always backed by concrete evidence, the knowledge of such factors may ultimately lead to well-informed decisions by patients that subsequently result in better health and therapy outcomes.

References


THYROID DISORDERS: A COMPREHENSIVE REVIEW

Self Evaluation Exercises

Select the best answer for each question and check your answers at the bottom of the page.

You do not need to submit this self-evaluation exercise with your participant sheet.

1. Goiter refers to the enlargement of the parathyroid glands.
   - True  - False

2. The incidence of thyroid diseases is higher among the male geriatric population.
   - True  - False

3. Thyroid hormones stimulate bone turnover leading to osteopenia in long-standing hyperthyroid condition.
   - True  - False

4. De Quervain’s thyroiditis is a malignant type of thyroid disease.
   - True  - False

5. Graves disease is the leading cause of hyperthyroidism in the US.
   - True  - False

6. Toxic adenoma refers to the malignant monoclonal nodular growth which results in autonomous hyperfunctioning of follicular thyroid cells.
   - True  - False

7. The antiarrhythmic drug amiodarone is rich in iodine and structurally resembles the thyroid hormone, T4, and stimulates its receptors.
   - True  - False

8. Follicular thyroid carcinoma is the most aggressive form of all thyroid malignancies.
   - True  - False

9. Thiocyanate inhibits iodide transport potently. There are two proposed actions of thiocyanate on the thyroid gland.
   - True  - False

10. Gestation hyperthyroidism is characterized by the presence of antimicrosomal antibodies and manifests clinically as transient thyrotoxicosis, hypothyroidism, or transient thyrotoxicosis followed by hypothyroidism.
    - True  - False