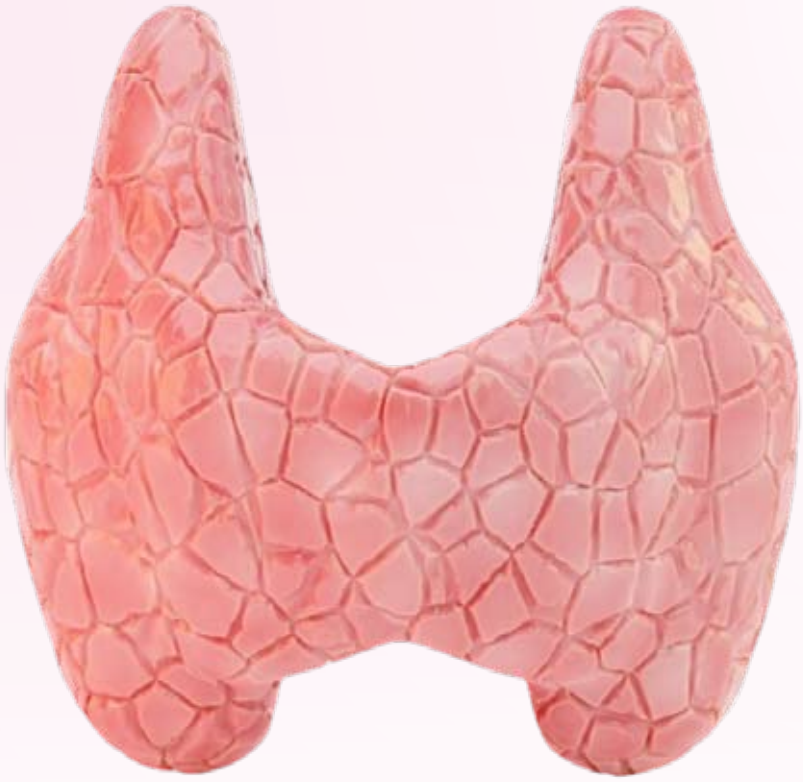
SAFES

CLINICAL PRACTICE RECOMMENDATIONS FOR THE MANAGEMENT OF

HYPOTHYROIDISM AND HYPERTHYROIDISM



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SAFES Clinical Practice Recommendations for the Management of Hypothyroidism and Hyperthyroidism

HYPOTHYROIDISM

Introduction

Hypothyroidism is a disorder characterized by the deficiency of thyroid hormones due to their insufficient synthesis, which in turn results in a generalized slowing down of metabolic processes.[1] Patients with hypothyroidism can have various clinical presentations, ranging from severe symptoms to none at all, and can vary with age and sex. Common symptoms in adults include fatigue, lethargy, cold intolerance, weight gain, constipation, voice changes, and dry skin.[2] Diagnosis of hypothyroidism requires laboratory testing due to the nonspecificity of symptoms.[3] The treatment goals for hypothyroidism are to alleviate symptoms and maintain TSH levels within the reference range. Oral Levothyroxine (LT4) is the preferred treatment option because of its effectiveness, safety, and convenience.[3] If left untreated, hypothyroidism can result in several complications, including hypertension, dyslipidemia, infertility, cognitive impairment, and neuromuscular dysfunction.[1]

Definition

Overt or clinical primary hypothyroidism is defined by TSH levels above the reference range and tetraiodothyronine (T4) and triiodothyronine (T3) below the reference range. Mild or subclinical hypothyroidism, often a symptom of early thyroid failure, is defined by TSH levels above the reference range and T3 and T4 levels within the normal range.[3]

Table 1: Prevalence of hypothyroidism in South Asian countries

Country	Hypothyroidism	Subclinical hypothyroidism
India[6]	10.95%	8.02%
Sri Lanka[7]	6.1%	9.4%
Bangladesh[8]	3.80%	3.46%
Pakistan[9]	4.1%	5.4%
Afghanistan[10]	12%	_

Epidemiology

The prevalence of hypothyroidism ranges from 0.2% to 1.3% in iodine-sufficient parts of the world.[5] Table 1 summarizes the prevalence of hypothyroidism and subclinical hypothyroidism in major South Asian countries.

Etiology

Hypothyroidism is either primary (caused by a lack of thyroid hormone), secondary (caused by a lack of TSH), or tertiary (caused by a lack of thyrotropin-releasing hormone). Central (including secondary and tertiary) are uncommon[2] Over 99% of affected patients suffer from primary hypothyroidism.[11]

Hypothyroidism

In regions of the world with sufficient iodine levels, Hashimoto's (autoimmune) thyroiditis is the primary cause of hypothyroidism, primarily affecting women.[2] Other causes of hypothyroidism include radioiodine therapy for hyperthyroidism, surgical removal of the thyroid gland, and certain medications that either suppress thyroid function or cause thyroid inflammation. Additionally, congenital absence of the thyroid gland or inborn defects in thyroid hormone production (dyshormonogenesis) can also lead to hypothyroidism. (Table 2). Although most cases of autoimmune thyroiditis lead to hypothyroidism, mild elevation of TSH levels in patients usually results in temporary rather than permanent hypothyroidism.[12]

Table 2: Causes of Hypothyroidism[2]

Primary hypothyroidism

- Chronic autoimmune thyroiditis (also known as Hashimoto's thyroiditis)
- Iodine: Severe iodine deficiency, mild and severe iodine excess
- Drugs: Amiodarone, lithium, tyrosine kinase inhibitors, interferon-alfa, thalidomide, monoclonal antibodies (e.g., ipilimumab and nivolumab), antiepileptic drugs (eg, valproate), drugs for second-line treatment of multidrug-resistant tuberculosis
- Iatrogenic: Radioiodine treatment (eg, for Graves' disease or toxic nodular disease), hemithyroidectomy, radiotherapy, or surgery in the neck or head region
- Transient thyroiditis: Viral (De Quervain's syndrome), post-partum, silent thyroiditis, destructive thyroiditis
- Thyroid gland infiltration:*—infectious (e.g., mycoplasma), malignant (e.g., thyroid malignancy, lymphoma, metastasis of malignancy elsewhere), autoimmune (e.g., sarcoidosis), inflammatory (e.g., Riedels's thyroiditis)
- Genetic*—autoimmunity-related genes (e.g., HLA class I region, PTPN22, SH2B3, and VAV3), general and thyroid-specific genes (e.g., FOXE1, ATXN2, and PDE8B)

Central hypothyroidism

- Pituitary tumors (secreting or non-secreting)
- Pituitary dysfunction (e.g., Sheehan's syndrome)
- Hypothalamic dysfunction (e.g., post-traumatic)
- Resistance to thyroid-stimulating hormone (TSH) or thyrotropin-releasing hormone
- Drugs (e.g., dopamine, somatostatins, glucocorticosteroids, and retinoid X receptor selective ligands)
- Increased TSH concentration due to leptin stimulation†

Peripheral (extra-thyroidal) hypothyroidism

- Consumptive hypothyroidism
- Tissue-specific hypothyroidism due to decreased sensitivity to thyroid hormone (eg, mutations in MCT8 [also known as SLC16A2], SECISBP2, THRA, THRB)

Pathophysiology

The thyroid gland synthesizes T4 and T3 hormones by utilizing iodide obtained from food or metabolic processes. It is estimated that about 100 ×g of iodide intake per day is necessary for the adequate production of thyroid hormones. Thyroid epithelial cells possess a specialized Na/I symporter, which facilitates the uptake of iodide from plasma, allowing for up to 30-40 times greater concentration of iodide within the thyroid gland for adequate thyroid hormone synthesis. Subsequently, thyroid peroxidase catalyzes the oxidation of iodide to iodine, and a series of organic reactions within the gland lead to the production of T4 and T3 hormones. T3 can also be produced in other organs like the pituitary, liver, and kidney by removing iodine from T4.

The T3 hormone is the most biologically active thyroid hormone, exhibiting 3-5 times higher potency than T4, which primarily acts as a pro-hormone. Both T3 and T4 are stored in the thyroglobulin protein within the thyroid gland and are released into circulation in response to pituitary-derived thyrotropin (TSH) stimulation. The human body typically produces approximately 90-100 ×g of T4 and 30-35 ×g of T3 per day. The majority of T3 in humans (80%) is derived from peripheral metabolism of T4, while only 20% is directly secreted by the thyroid gland. T4 strongly binds to TBG (75%), weakly to TBPA (20%), and poorly to albumin (5%). T3 strongly binds to TBG and weakly to albumin, but not to TBPA. Normal serum levels for T4 and T3 are around 8 ×g/dL and 130 ng/dL, respectively. Almost all T4 and T3 in the bloodstream are bound to plasma proteins, with only a small fraction of free T4 (~2 ng/dL) and T3 (~0.3 ng/dL) being biologically active.

Figure 1. Pathway for secretion of thyroid hormones[13]

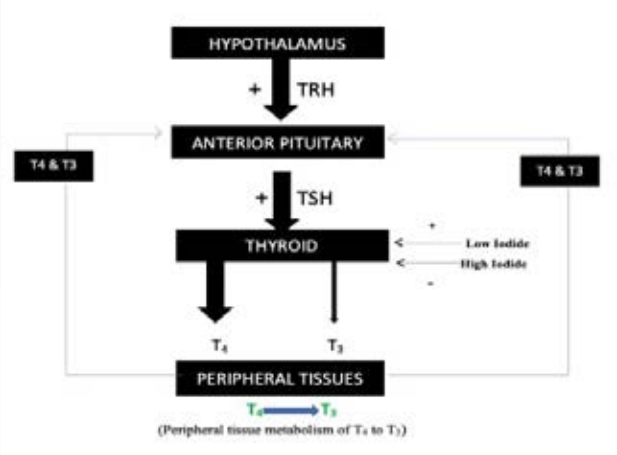


Table 3. Factors that alter T4 and T3 binding in serum[14]		
Increased TBG	Decreased TBG	Binding inhibitors
Inherited	Inherited	Salicylates
Pregnancy	Androgens	Furosemide
Neonatal state	Anabolic steroids	Free fatty acids
Estrogens	Glucocorticoids	Phenytoin
Hepatitis	Severe illness	Carbamazepine
Porphyria	Hepatic failure	NSAIDs (variable, transient)
Heroin	Nephrosis	Heparin
Methadone	Nicotinic acid	
Mitotane	L-Asparaginase	
5-Fluorouracil		
SERMS (e.g., tamoxifen, raloxifene)		
Perphenazine		

Binding proteins in serum, including T4-binding globulin (TBG), transthyretin, and T4-binding prealbumin, as well as albumin to a lesser extent, bind specifically with T4. As 99.97% of T4 is bound to these proteins, changes in binding due

to factors unrelated to thyroid disease can affect total T4 levels in serum. (Table 3).[14] Likewise, T3 is bound to serum proteins, mainly TBG, although to a lesser level (99.7%). Measuring serum T3 (total or free) is not useful in hypothyroidism as the remaining functional thyroid tissue is hyperstimulated by increased TSH and type 2 iodothyronine deiodinase up-regulation, resulting in typically normal T3 levels. [15] Hence, relying on a normal TSH and free T4 to make clinical judgments may lead to complications in most cases.[15]

Clinical features

Common symptoms

The symptoms of hypothyroidism are often insidious in onset. Common clinical manifestations of hypothyroidism include constipation, dryness of skin and hair with sparsing of hair, edema, cold intolerance, fatigue, myalgias, voice changes, and menstrual irregularities (Figure 2).[14]

Less common symptoms of hypothyroidism

The less frequently observed manifestations of hypothyroidism include carpal tunnel syndrome, sleep apnea, pituitary hyperplasia with or without hyperprolactinemia and galactorrhea, and hyponatremia that may develop within weeks of the onset of profound hypothyroidism.[14]

Systemic manifestations

Hypothyroidism affects almost all major organ systems. . Table 4 delineates systemwise manifestations.[2]

Figure 2. Common symptoms and signs associated with hypothyroidism[4]

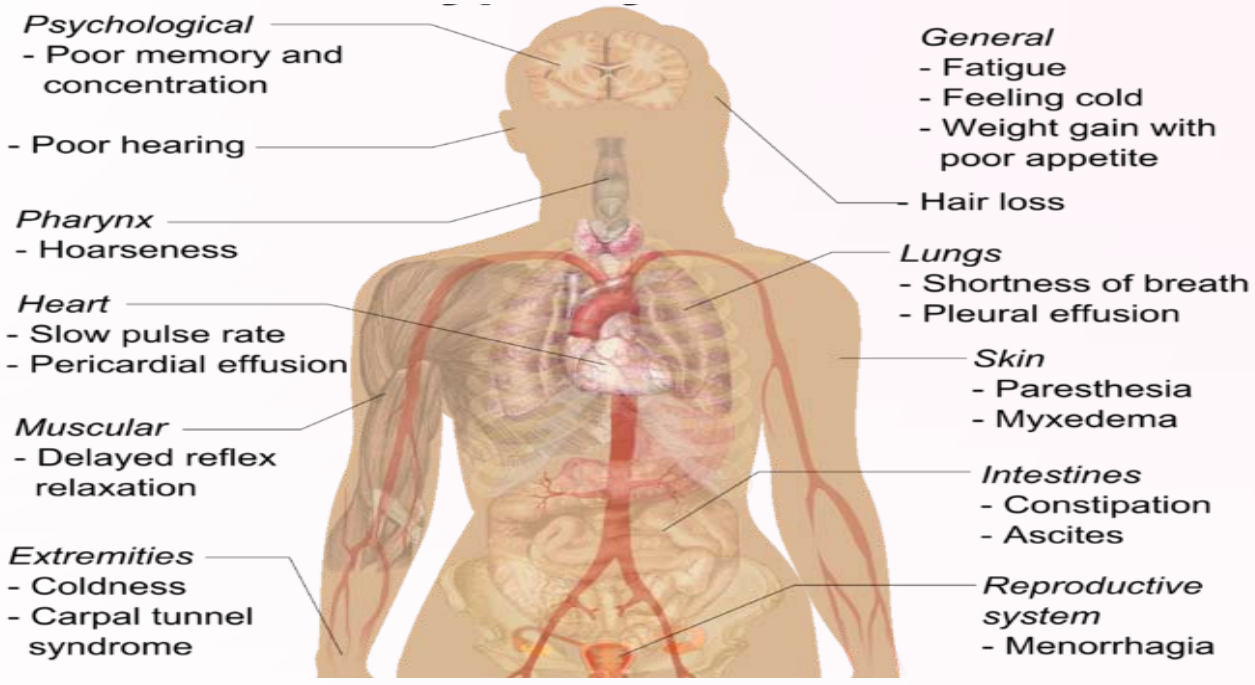


Table 4. Clinical presentation of hypothyroidism		
System	Symptoms	Signs
General metabolism	Weight gain, cold intolerance, fatigue	Increase in body-mass index, low metabolic rate, myxedema*, hypothermia*
Cardiovascular	Fatigue on exertion, shortness of breath	Dyslipidemia, bradycardia, hypertension, endothelial dysfunction or increased intima-media thickness*, diastolic dysfunction*, pericardial effusion*, hyperhomocysteinemia*, electrocardiogram changes*
Neurosensory	Hoarseness of voice, decreased taste, vision, or hearing	Neuropathy, cochlear dysfunction, decreased olfactory and gustatory sensitivity
Neurological and psychiatric	Impaired memory, paresthesia, mood impairment	Impaired cognitive function, delayed relaxation of tendon reflexes, depression*, dementia*, ataxia*, Carpal tunnel syndrome and other nerve entrapment syndromes*, myxedema coma*
Gastrointestinal	Constipation	Reduced esophageal motility, non-alcoholic fatty liver disease*, ascites (very rare)
Endocrinological	Infertility and subfertility, menstrual disturbance, galactorrhoea	Goiter, glucose metabolism dysregulation, infertility, sexual dysfunction increased prolactin, pituitary hyperplasia
Musculoskeletal	Muscle weakness, muscle cramps, arthralgia	Creatine phosphokinase elevation, Hoffman's syndrome*, osteoporotic fracture* (most probably caused by overtreatment)
Hematological	Bleeding, fatigue	Mild anemia acquired von Willebrand disease*, decreased protein C and S*, increased red cell distribution width*, increased mean platelet volume
Skin and hair	Dry skin, hair loss	Coarse skin, loss of lateral eyebrows*, yellow palms of the hand*, alopecia areata*
Electrolytes and renal function	Deterioration of kidney function	Decreased estimated glomerular filtration rate, hyponatremia*
*Uncommon presentation		

Diagnosis

The measurement of TSH is the primary diagnostic test for identifying thyroid dysfunction and monitoring thyroid hormone replacement therapy in primary hypothyroidism.[14] The reference range for TSH is typically 0.4 to 4.5 mIU/L, with the lower limit being 0.4 mIU/L. The evaluation of free thyroxine (FT4) levels is essential in distinguishing clinical (low FT4) from subclinical (normal FT4) hypothyroidism. However, the routine assessment of total T3, total T4, or FT3 levels is not recommended. Although thyroid peroxidase antibody (TPOAb) testing may not be diagnostic for hypothyroidism, it can be useful in identifying autoimmune causes of thyroid dysfunction. Furthermore, thyroid ultrasonography is primarily utilized for evaluating palpable thyroid nodules, and it is not a routine diagnostic test for hypothyroidism.[16] Table 5 is a detailed guide to the diagnosis of hypothyroidism.

Table 5. Laboratory Values in Hypothyroidism[17]			
TSH level	Free T_4 level	Free T_3 level	Likely diagnosis
High	Low	Low	Primary hypothyroidism
High	Normal	Normal	Subclinical hypothyroidism
High	High	High	Peripheral thyroid hormone resistance
Low	Low	Low	Pituitary thyroid deficiency or recent withdrawal of thyroxine after excessive replacement therapy

Associated laboratory abnormalities may suggest a diagnosis of hypothyroidism. Abnormalities which may require investigating for hypothyroidism include hyponatremia, macrocytic anemia, and elevated creatine kinase levels. Hypothyroidism may also result in an abnormal lipid profile.[3]

Treatment

LT4 therapy is considered the primary treatment for hypothyroidism due to its long-standing use, low cost, excellent intestinal absorption, extended serum half-life, and ease of administration.[14]

- The primary aims of LT4 replacement are:[14]
  - » To provide symptomatic relief
  - » To normalize thyroid function tests
  - » To maintain patients in a euthyroid state
- When establishing a starting dose of LT4 for hypothyroidism treatment, it is important to take into account several patient-specific factors, such as weight, lean body mass, pregnancy, underlying cause of hypothyroidism, degree of TSH elevation, age, presence of comorbidities, and particularly, the presence of cardiovascular disease.[19]
- Patients with hypothyroidism having low endogenous thyroid activity require LT4 dosages of 1.6 1.8 ×g/kg body weight.[19]
- LT4 administration be scheduled either 60 minutes before breakfast or at bedtime, provided that it is feasible. This ensures optimal and consistent absorption, as co-administration of food and LT4 can reduce LT4 absorption.[19]
- The recommended protocol for monitoring thyroid function in patients with hypothyroidism includes measuring serum TSH levels 4 8 weeks after initiating treatment or adjusting the dose. After determining an appropriate replacement dose, periodic TSH measurements should be taken at 6 months and then annually, or more frequently if clinically indicated.[14]
- For optimal benefit LT4 should be administered daily, however, missed doses should be administered as soon as they are recognized.[19]
- In special circumstances, a weekly cumulative dose has been advocated.
- Patients receiving LT4 replacement for hypothyroidism should have blood drawn before dosing so that serum-free T4 levels may be assessed.[15]

Prescribing LT3

LT3 is recommended for patients with hypothyroidism who remain symptomatic despite being biochemically euthyroid. LT3 monotherapy is currently limited to the treatment of severe hypothyroidism with myxedema coma. Short-term LT3 therapy may also be beneficial in patients with differentiated thyroid cancer who are being tapered off LT4 prior to radioiodine therapy to minimize symptomatic hypothyroidism.[12]

When to refer to an Endocrinologist / Thyroid specialist

Although most general practitioners are capable of diagnosing and treating hypothyroidism, the following circumstances call for a referral to an endocrinologist:[14]

- Children and infants
- Patients in whom it is difficult to render and maintain a euthyroid state
- Pregnancy
- Women planning conception
- Cardiac disease
- Presence of goiter, nodule, or other structural changes in the thyroid gland
- Presence of other endocrine diseases such as adrenal and pituitary disorders
- Unusual constellation of thyroid function test results
- Unusual causes of hypothyroidism such as those induced by agents listed in Table 10.

Screening and aggressive case finding for hypothyroidism

The recommendations for screening asymptomatic individuals with thyroid dysfunction are summarized in Table 6.

Table 6: Recommendations of Six Organizations regarding screening of asymptomatic adults for thyroid dysfunction[14]

Organization	Screening recommendations
American Thyroid Association	Women and men > 35 years of age should be screened every 5 years
American Association of Clinical Endocrinologists	Older patients, especially women, should be screened.
American Academy of Family Physicians	Patients ≥60 years of age should be screened.
American College of Physicians	Women ≥50 years of age with an incidental finding suggestive of symptomatic thyroid disease should be evaluated.
U.S. Preventive Services Task Force	Insufficient evidence for or against screening
Royal College of Physicians of London	Screening of the healthy adult population unjustified

Screening is recommended for the following high-risk groups:[20]

- All newborn infants (mandatory in many states)
- Downs syndrome
- Pregnant women with or without goiter
- Have a strong family history of thyroid disease
- A personal history of thyroid dysfunction
- Have an autoimmune disease, such as Type 1 Diabetes
- Are taking lithium
- Have Depression
- Have elevated lipid levels
- Are found to have a thyroid nodule
- Those with hyponatremia, hyperprolactinemia, or goiter

Refractory Hypothyroidism

Refractory primary hypothyroidism is defined as evidence of biochemical or clinical hypothyroidism, such as a serum level of TSH beyond the upper limit of the goal level, which is generally 4.5 mU/L after a 6-week interval following the last increase in dosage, and/or unresolved hypothyroid symptoms despite increasing doses of LT4 above 1.9 ×g/kg/day. It is important to note that further increases in LT4 dosage may not always be the best approach, as excessive dosages have been linked to adverse cardiovascular outcomes and bone health. Clinicians should verify compliance and investigate reasons for poor absorption or a higher need for LT4 in cases where unexpectedly high doses of LT4 are required (Table 7).21

Table 7. Causes of treatment-refractory hypothyroidism

• Decreased bioavailability
• Poor adherence to, or tolerability of, drug therapy
• Patient-related factors or behavior o Proton-pump inhibitor therapy o Gastric infection with Helicobacter pylori o Intestinal malabsorption of levothyroxine (LT4)
• Luminal factors (e.g., food, coffee, and medications)
• Intramural factors (e.g., short bowel syndrome, lactose intolerance, gluten enteropathy, inflammatory bowel disease, infiltrative enteropathy, infection with Giardia)
• Increased need for LT4 o Weight gain o Pregnancy o Increased metabolism of thyroxine
• Other factors that can alter serum levels of TSH o Addison's disease o Altered regulation of the hypothalamic-pituitary-thyroid axis o TSH heterophile antibodies o Inappropriate tablet storage

TSH thyroid-stimulating hormone

- The most frequent treatment for resistant hypothyroidism is to increase the LT4 dose or change formulation until target TSH levels are reached and symptoms are managed.[22]

Myxedema Coma

- Myxedema coma is a life-threatening endocrine emergency that can occur in patients with severe, untreated hypothyroidism. In addition to age, several factors have been identified as potential predictors of mortality in patients with myxedema coma. These include concomitant cardiovascular disease and treatment with high-dose LT4 replacement therapy.[23]

- Sepsis, cerebrovascular accidents, and congestive heart failure are recognized precipitating factors of myxedema coma. The use of sedatives and antidepressants may contribute to the development of myxedema coma by masking the symptoms of hypothyroidism. An excessive diuretic use for hypertension and edema resulting in hyponatremia is not a direct cause of myxedema coma, but it may exacerbate the underlying hypothyroidism. Therefore, clinicians should be aware of the risk factors and precipitating factors associated with myxedema coma and manage patients accordingly.[20]

- Elderly individuals with undertreated primary hypothyroidism and comorbid diseases may be particularly susceptible to decompensation that leads to the onset and progression of this life-threatening condition.[23]

- In addition to coma, hypothermia, bradycardia, hypotension, ileus, hypoventilation with hypercapnia and respiratory acidosis are possible complications. [23]
- Pericardial effusions may be frequently associated.[23]
- General recommendations for supportive care include intensive monitoring of vital signs, slow and careful external rewarming with heating blankets, correction of fluid and electrolyte imbalances, avoidance of hypnotics and sedatives, empirical treatment of suspected underlying infections, and mechanical ventilation if needed.[23]
- Dosage and composition recommendations for treating myxedema coma vary. A loading dosage of 200 300 ×g of intravenous LT4 may be followed by 50 ×g daily.[23]
- Depending on the risk of cardiovascular disease, a loading dosage of 5 25 ×g of LT3 may be delivered concomitantly followed by 2.5 5 ×g every eight hours until clinical improvement is visible.[23]
- Intravenous hydrocortisone is recommended at a dose of 50 100 mg every 8 hours while testing for adrenal insufficiency is being performed.[23]
- Since intravenous LT4 is not commonly available in India, most hospitals substitute parenteral therapy with crushed LT4 tablets administered through a nasogastric tube. The initial dose typically ranges from 300 500 ×g, followed by 100 ×g per day. However, the route of administration is unfavorable because it not only raises the risk of irregular absorption, especially in patients with stomach atony the potential for aspiration if the airway is not protected.[20]

Special population

Hypothyroidism in elderly

- Hypothyroidism is more common among the elderly.[23]
- The typical range of TSH levels in the elderly is higher due to age-related changes.[23]
- The National Health and Nutrition Examination Survey III (NHANES III) study found that the upper limit of the reference range (97.5% confidence interval) for TSH increases from 3.56 mU/L in individuals aged 20-29 years to 7.9 mU/L in those over 80 years old.[23]
- Consequently, it will be crucial to evaluate these age-related variations in TSH levels when diagnosing hypothyroidism.[23]

Symptoms and signs[23-24]

- Elderly patients with hypothyroidism may present with less specific symptoms compared to younger patients with thyroid hormone deficiency
- Hypogeusia and dysgeusia, hearing loss, and ataxia are more prevalent in elderly people. Complaints of cold intolerance, weight gain, paresthesias, and muscle cramps were less common.

- The clinical manifestations of hypothyroidism in the elderly may include bradycardia, diastolic hypertension, pallor, dry skin, coarse hair, hoarseness, dysarthria, delayed deep tendon reflexes, and mental state abnormalities.
- Common comorbid in elderly such as cardiovascular, neuropsychiatric, dermatologic, or rheumatologic disorders worsen the severity of specific findings.

Treatment of hypothyroidism in the elderly

- LT4 is recommended as the first-line treatment for hypothyroidism in the elderly, however, it should be used with caution.[25]
- It is recommended to initiate LT4 therapy at low dosages and gradually increasing the dose in response to serum TSH levels and higher serum TSH targets may be warranted considering the higher reference range for TSH .[19]
- Decreases in LT4 requirements occur as patients age and follow significant weight loss.[25]
- Patients aged 50 60 years without evidence of coronary heart disease (CHD) may be started on doses of 50 ×g daily, regardless of the severity of their hypothyroidism. In patients with established CHD, the initial dose is typically lowered to 12.5–25 ×g/day.[14]
- It is recommended to gradually increase the dosage by 25 ×g within 2–3 weeks based on the patient's complaints or improvements while keeping family members informed of any adverse reactions or symptoms.[25]
- Clinical monitoring for the onset of anginal symptoms is essential.[25]

Pregnancy and hypothyroidism

- Untreated hypothyroidism during pregnancy can negatively affect both maternal and fetal outcomes, particularly in TPOAb-positive women.[14] Refer to Table 8 for a list of potential adverse events.

Table 8: Effects of hypothyroidism in pregnancy[26]

Maternal	Fetal	Neonatal
Anemia and CHF	Cognitive impairment	Hyperbilirubinemia
Pre-eclampsia	Neurological abnormalities	Respiratory distress
Placental abnormalities	Developmental abnormalities	
Low Birth Weight infants	Congenital Hypothyroidism	
Post-partum hemorrhage		
Myopathy		

- Women with a positive TPOAb may have a greater risk of miscarriage in the first trimester, premature birth, and cognitive impairment in the offspring.[14]
- This risk may be a result of diminished thyroid functional reserve brought on by persistent autoimmune thyroiditis, which can lead to mild hypothyroidism.[14]

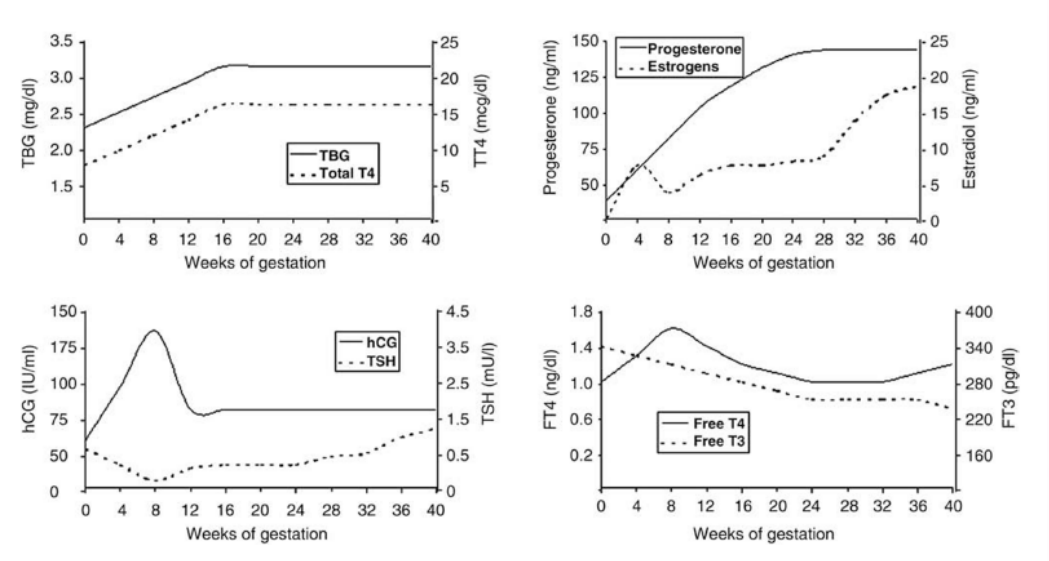
Diagnosis of maternal hypothyroidism

- Assessing thyroid function during pregnancy can be challenging due to physiological changes such as increased TBG, placental

deiodinase activity, urinary iodine excretion, and elevated hCG secretion. These changes result in a downward shift of TSH reference intervals, making it difficult to interpret maternal thyroid function tests. Applying TSH reference intervals for non-pregnant women to pregnant women can lead to under-diagnosis of hypothyroidism or over-diagnosis of hyperthyroidism.[27]

- The ATA 2017 guideline recommends using pregnancy and trimester-specific TSH reference ranges that are developed from a local population that is iodine-sufficient, TPO antibody-negative, and free from underlying thyroid disorders. If locally derived reference ranges are unavailable, the lower reference range of TSH can be reduced by approximately 0.4 mU/L in the first trimester of pregnancy (Figure 3).[28]
- The upper reference range is reduced by approximately 0.5mU/L and this usually corresponds to a TSH upper reference limit of 4.0mU/L. This reference limit should generally be applied beginning with the late first trimester, weeks 7–12, with a gradual return towards the nonpregnant range in the second and third trimesters.[28]
- In addition to measuring TSH, pregnant women should have their total T4 or a free T4 index measured to determine their thyroid health. Because of the large heterogeneity in free T4 assay results, direct immunoassay measurement should only be used when method- and trimester-specific reference ranges are available.[14]
- Total T4 is generally preferred over free T4 during pregnancy following adjustment by a factor of 1.5 to compensate for the anticipated

Figure 3: Variation in serum levels of thyroid function test and pregnancy-related hormones according to course of gestation.[30]



TBG rise. Pregnancy-specific and preferably trimester-specific reference ranges for all thyroid function tests is necessary, but especially for the most often used assays, TSH, free T4, total T4, and total T3.[29]

Preconception management of hypothyroidism[31]

- The purpose of preconception management is to treat hypothyroidism, provide pre-pregnancy counseling, and raise the LT4 dose at conception before conception.
- Most women with hypothyroidism will require an increase in LT4 dose to satisfy gestational demands in the absence of a functioning thyroid gland.
- Women newly diagnosed with hypothyroidism should be started on full replacement doses of LT4 (0.8 1.6 ×g/kg/d) and should be counseled on the importance of treatment adherence and the necessity to maximize thyroid hormone replacement before conception.
- The preconception TSH goal for LT4 -treated women should be between the lower reference limit and 2.5 mU/L.
- LT4-treated women should get a thyroid function test and increase their dose after pregnancy is established before the blood test result is available.

Management of hypothyroidism during pregnancy

- According to the American Thyroid Association's (ATA) guidelines for the management of thyroid illness during pregnancy, the TSH range for each trimester should be defined within the medical system providing care, with a generalized range as follows: 0.1-2.5 mIU/L for the first trimester, 0.2-3.0 mIU/L for the second trimester, and 0.3-3.0 mIU/L for the third trimester (Table 9).[19]

Table 9: Trimester-specific TSH reference range[26]

Guidelines	Country	Trimester specific recommended TSH ref range
ITS Guidelines (2012)	India	• 1st - 2.5 mIU/L • 2nd - 3.0mIU/L • 3rd - 3.0 mIU/L
ETA Guidelines (2014)	European	• 1st - 2.5 mIU/L • 2nd - 3.0mIU/L • 3rd - 3.0 mIU/L
ATA Guidelines (2017)	American	• Use locally derived Reference ranges from a specified Pregnant population • If the above is not available use an upper TSH reference limit of 4.0 mIU/L

- Thyroid function should be evaluated every 4–6 weeks during the first and second trimesters to determine if additional LT4 dose modifications are needed.[14]
- During the third trimester, a reevaluation of thyroid function is also required. After birth, women's LT4 requirements normally revert to their pre-pregnancy levels.[14]

Need for thyroid replacement therapy in pregnant women with SCH

- Several studies, both prospective and retrospective, have demonstrated a correlation between moderately elevated maternal TSH

levels and an increased risk of pregnancy complications, particularly in TPOAb-positive women. However, only a limited number of studies have investigated the effects of LT4 treatment on pregnancy outcomes in these women. A randomized controlled trial showed potential benefits of LT4 intervention initiated at 9 weeks gestation with a reduction in unfavorable pregnancy outcomes but only among TPOAb-positive women with mild hypothyroidism, which is defined as a TSH level greater than 2.5 mU/L.[28]

- TPOAb are present in half of the women with subclinical hypothyroidism, which increases the likelihood of poor outcomes. TPOAb status should be checked in pregnant women with TSH over 2.5 mIU/L.[32]
- If they test positive for TPOAb, these women should be administered LT4 to achieve a TSH level in the lower half of the trimester-specific range. TPOAb-negative women should be treated if their TSH is higher than 10.0.[32] In making its decision, the task committee recognizes the very low risk of starting low-dose LT4 treatment and the evidence supporting treatment for each subgroup may vary by TPOAb status.[28]
- Typically, only 50 μg/d is needed to effectively treat subclinical hypothyroidism in women.[28]

Treatment of women with isolated hypothyroxinemia in pregnancy[28]

- Observational studies conducted over 12, 24, and 32 weeks have found that persistent hypothyroxinemia in pregnant women can result in impaired infant neurodevelopment. However, increasing FT4 concentrations during pregnancy did not improve infant growth.
- Currently, there are only two randomized, prospective trials that have investigated the use of LT4 therapy in women with low FT4 levels, administered at 13 and 17 weeks gestation. Both studies reported no significant improvement in cognitive development following LT4 administration, despite the intervention being initiated after the first trimester.

Role of iodine

- During pregnancy, thyroid hormone synthesis, renal iodine excretion, and fetal iodine needs increase, necessitating higher dietary iodine intake. Adequate iodine intake before and during pregnancy helps women cope with the increased demand for thyroid hormones during pregnancy, and breastfeeding women also require increased dietary iodine.[28]
- Maternal iodine deficiency can impair thyroid hormone synthesis, leading to elevated pituitary TSH production, maternal, and fetal goiter. In areas with severe iodine deficiency, up to 30% of pregnant women may develop thyroid nodules, and severe iodine shortage in pregnant women can increase the risk of pregnancy loss, stillbirth, perinatal, and infant mortality.[28]
- Normal thyroid hormone levels are essential

for neuronal migration, myelination, and other embryonic brain processes. Iodine deficiency during pregnancy can impair thyroid hormone production, leading to negative consequence including impaired cognitive performance in offspring. Cretinism, which causes intellectual disability, deaf-mutism, and motor stiffness, may develop in children of iodine-deficient mothers.[28]

- Iodine is crucial for thyroid hormone production and can be obtained from dietary sources and vitamin/mineral supplements. The U.S. Institute of Medicine recommends different daily iodine intake targets based on a woman's pregnancy and lactation status: 150 ×g/day for women contemplating pregnancy, 220 ×g/day for pregnant women, and 290 ×g/day for lactating women. The World Health Organization recommends a daily iodine intake of 250 ×g/day for pregnant and lactating women.[28]

SUBCLINICAL HYPOTHYROIDISM

Introduction

Subclinical hypothyroidism (SCH) is characterized by elevated serum TSH levels, despite circulating T4 and T3 levels within the normal range. There are two categories of SCH based on the degree of TSH elevation:[33]

- mildly increased TSH levels (4.0–10.0 mU/l) and
- more severely increased TSH value (>10 mU/l).

Etiology

The most common cause of SCH is chronic autoimmune thyroiditis (Hashimoto's disease or autoimmune atrophic thyroiditis). Other endogenous factors that can cause SCH include sub-acute thyroiditis and chronic autoimmune thyroiditis. Exogenous factors that can cause SCH include inadequate therapy with the thyroid replacement, the effect of antithyroid drugs, thyroidectomy, thyroid infiltration, occupational exposure to pesticides, chronic excessive iodine intake, external radiation, and radioiodine therapy.[34-35]

Clinical features

SCH is asymptomatic, but in cases can manifest symptoms of hypothyroidism. It is crucial to evaluate hypothyroid symptoms, as this determines if thyroid replacement therapy needs to be initiated (Table 10).[36]

Table 10. Symptoms of subclinical hypothyroidism[36]

- Integumentary: Dry skin, hair loss, loss of outer 1/3rd of eyebrows, facial puffiness.
- Gastrointestinal: Constipation, dysphagia, loss of appetite, weight gain, cholelithiasis
- Cardiovascular: Diastolic hypertension, bradycardia, pericardial effusions
- Neurological: Decreased attention span, pseudodementia, mononeuropathies (most common carpal tunnel syndrome)
- Musculoskeletal: Muscular weakness, cramps, stiffness, fatigue
- Reproductive: Irregular periods, decreased libido

Management of subclinical hypothyroidism

For asymptomatic patients with TSH levels between 4.5 and 10 ×U per mL, repeat testing every 6 to 12 months is recommended. The available evidence does not support early treatment of SCH in these patients. Therefore, the use of LT4 therapy is not recommended for this patient population. In individuals with hypothyroidism and TSH levels between 4.5 and 10 ×U per mL, the evidence is insufficient to justify therapeutic intervention.[37]

If a high serum TSH concentration is confirmed on repeat tests and serum FT4 is within the reference range, the patient should be assessed for signs and symptoms of hypothyroidism, past treatment for hyperthyroidism (radioiodine, partial thyroidectomy), thyroid gland enlargement, or family history of thyroid disease. Lipid profiles should be checked. Women who

are pregnant or intend to become pregnant in the near future deserve special consideration.[38]

There is currently insufficient evidence to support routine TPOAb testing in the diagnosis and management of SCH. A TPOAb positivity may indicate an autoimmune etiology for thyroid dysfunction and predict a higher likelihood of developing overt hypothyroidism. The presence or absence of TPOAb does not affect the diagnosis of SCH based on serum TSH levels or the efficacy of therapy.[38] Factors that may favor the treatment of SCH include the presence of symptoms listed in the Table 11.[39]

Treatment of patients with SCH between 2.5 and 4.5 mIU/L

- There is no clinical evidence to support the treatment of patients with SCH who have TSH levels between 2.5 and 4.5 mIU/L. However, there may be exceptions for pregnant women with TSH values between 2.5 and 5.0 mIU/L who are negative for anti-thyroid antibodies. These women are at an increased risk of complications, such as pregnancy loss, spontaneous miscarriage before 20 weeks gestation, and stillbirth after 20 weeks.[14]

Table 11. Factors favoring levothyroxine therapy in subclinical hypothyroidism[39]
• TSH levels > 2 times the upper limit of normal or > 8 mIUI/L
• Progressive rise in TSH
• Goiter
• Positive antithyroid antibodies
• Pregnancy or planning pregnancy
• Infertility or ovulatory dysfunction
• Dyslipidemia
• Established CVD or risk factors for CVD
• Clinical symptoms of hypothyroidism
• Bipolar disorder, depression
• Childhood and adolescents with short stature

Treatment of adults (<65 years of age)[40]

- All younger patients with TSH ▌ 10 mU/L should be treated to reduce the risk of long-term cardiovascular complications, progression to overt hypothyroidism (OH), and mortality.
  - » Individuals with TSH 4.5 9.9 mU/L who are healthy and asymptomatic do not require treatment.
  - » Individuals with serum TSH ▌7.0 mU/L with pre-existing cardiovascular disease or high cardiovascular risk, due to the association with a higher risk of fatal and non-fatal CHD and stroke may be considered for treatment.
  - » Individuals with TSH 4.5 9.9 mU/L at a higher risk of progression to OH (female gender, a progressive increase of TSH levels, positive TPOAb) can be considered for treatment.

Treatment of elderly (≥65 years of age)

- Elderly patients with SCH should be treated with caution preferably by an endocrinologist, as this subgroup of patients is at a higher risk of LT4 overtreatment and are more susceptible to adverse consequences, such as reduction of bone mineral density, heart failure, and atrial fibrillation.[33]

- Observation without treatment should be the strategy in patients greater than 80–85 years old with SCH and serum TSH less than or equal to 10 mIU/L.[33]

- A recently published 2022 study has shown that LT4 treatment of SCH (4·5 7·0 mIU/L) in individuals aged▌ 65 years did not improve the symptoms of hypothyroidism and cardiac and bone parameters.
- The data suggests that LT4 should be considered for individuals aged ▌65 years with SCH when TSH concentration is persistently 7 mIU/L or higher.[33]
- LT4 doses should be personalized according to age, comorbidities, and life expectancy in elderly aged ▌65 years.[41]

Existing guidelines on thyroid hormone replacement in SCH patients

Existing guidelines recommend thyroid hormone treatment for adults with TSH levels >10 mIU/L, however, treatment is recommended for the younger, symptomatic, or those with cardiovascular disease or antibodies to thyroid peroxidase having lower TSH levels.[42]

Follow-up and monitoring of untreated and treated SCH patients

Initial diagnosis of SCH should be confirmed by the measurement of TSH, T4, and TPO-Ab after 8–12 weeks. If thyroid function has normalized, then no further testing is required in asymptomatic individuals having negative thyroid autoantibodies or no goiter. However, if untreated SCH is persistent, thyroid function should be tested 6 monthly for the first 2 years and then yearly thereafter. If LT4 treatment is initiated in SCH patients, then serum TSH should be monitored at least annually thereafter.[33]

Guideline	Recommendations for treatment
National Institute for Health and Care Excellence (NICE) CKS guidelines, 2018[43]	• TSH >10 mIU/L: - Age <70 years, treat - Age ≥70 years, watch and wait • TSH 4-10 mIU/L: - Age <65 years with symptoms, consider trial - Age ≥65 years, watch and wait
European Thyroid Association (ETA), 2013[33]	• Age <70 years: - TSH >10 mIU/L, treat - TSH <10 mIU/L with symptoms, start a trial - TSH <10 mIU/L without symptoms, observe • Age >70 years: - TSH <10 mIU/L, observe - TSH >10 mIU/L, consider treatment if clear symptoms or high cardiovascular risk
American Thyroid Association (ATA), 2012[14]	• TSH >10 mIU/L, consider treatment • TSH <10 mIU/L, consider treatment if symptoms suggestive of hypothyroidism, positive antibodies to thyroid peroxidase, or evidence of atherosclerotic cardiovascular disease, heart failure, or risk factors for these diseases
British clinical practice guideline in 2019[42]	• Lack of benefit from thyroid hormone treatment in nearly all those with SCH (does not apply to pregnant or women trying to conceive, those with severe symptoms, or those younger than 30 years), and specifically that asymptomatic SCH patients or those with non-specific symptoms should not be treated. • The decision to initiate treatment should be individualized based on the degree of serum TSH elevation, symptoms, patient preference, and other factors.

Special conditions

Coronavirus disease – 2019

There is no information on how it affects individuals with hypothyroidism. As such patients with hypothyroidism are not at increased risk of viral infections in general and there is no association between hypothyroidism and the severity of viral infection. It is recommended that patients with hypothyroidism should continue taking their LT4 treatment as suggested. Pregnant patients with hypothyroidism should continue taking LT4 treatment. Patients with hypothyroidism and other comorbidities such as diabetes, cardiac disease, and hypertension are at high risk for severe COVID-19 infection and such patients need to take more precautions.[44]

Hypothyroidism with comorbidities

Dyslipidemia

The evidence is insufficient to recommend targeting treatment with LT4 to achieve low-normal TSH or high-normal T3 levels in patients with hypothyroidism who have dyslipidemia or are athyreotic. However, thyroid hormone replacement therapy is beneficial for patients with severe and mild SCH and dyslipidemia. Patients should have repeat serum TSH measurements 8 12 weeks after starting LT4 therapy, and the LT4 dose should be adjusted if necessary to ensure TSH falls into the reference range. If hypercholesterolemia or other dyslipidemia was present before starting LT4, it is worthwhile to recheck the serum lipid profile to assess improvement and determine if additional dyslipidemia therapy is necessary. At this point, it is also worthwhile to reevaluate hypothyroidism symptoms in individuals with SCH who were started on therapy for these symptoms.[33]

Hypertension

Subclinical or overt hypothyroidism is frequently associated with systolic and/or diastolic hypertension, which can have a negative impact on the cardiovascular system. Hence, early initiation of adequate thyroid replacement therapy with LT4 for an extended period of time may play a critical role in the majority of cases of hypertension reversal and may reduce cardiovascular risk factors.[45]

Obesity

Obesity and thyroid dysfunction are common conditions that often coexist. Clinicians should be aware of the higher prevalence of thyroid disorders in obese patients and consider testing for thyroid function in this population. Subclinical hypothyroidism is a common finding in obese individuals and can be challenging to diagnose. While treatment of overt hypothyroidism can lead to modest weight reduction in some patients, the primary goal of therapy is to restore normal thyroid hormone levels and alleviate symptoms. The use of thyroid hormones for weight loss in euthyroid individuals is not recommended due to potential adverse effect.[46]

Cardiovascular diseases

A cross-sectional survey was conducted on a population of 986 community-dwelling adults in Southern India to investigate the impact of

subclinical hypothyroidism on cardiovascular health. The Framingham score algorithm was used to calculate the ten-year risk of adverse cardiac events. The sample population had significant baseline rates of diabetes (19.5%), hypercholesterolemia (57.2%), and systolic hypertension (24%). Results indicated that subclinical hypothyroidism or increasing TSH levels did not have a significant impact on Framingham's 10-year risk. While lipid profiles did not differ between groups, there was a modest worsening of lipid profiles associated with increased TSH levels.[47]

The American Thyroid Association guidelines for hypothyroidism in adults recommend initiating thyroid hormone treatment for primary hypothyroidism when the serum TSH is above 10 mIU/L. For individuals with an increased CVD risk when the serum TSH levels are in the range of 4.5 10 mIU/L. While there are limited outcome data on treating patients with serum TSH 2.5 4.5 mIU/L, studies have demonstrated improved markers of atherosclerosis risk (lipids, endothelial function, and intima-media thickness) which supports consideration for treating of SCH with serum TSH values in this range.[48]

The American Thyroid Association guidelines recommend starting LT4 at a low dose for individuals with known CVD, gradually increasing as needed, and closely monitoring for the development of cardiac symptoms.[5] Currently, most international societal guidelines recommend individualizing treatment decisions based on patient age, degree of serum TSH elevation, symptoms, CVD risk, and other co-morbidities. Caution should be exercised when initiating LT4 treatment for SCH in elderly patients. It is important to note that specific reference intervals apply to certain subpopulations (such as the elderly and pregnant women), which may impact the decision to treat or withhold treatment with LT4.[48]

Depression

LT4 monotherapy in solid form, administered on an empty stomach, is the preferred treatment for hypothyroidism. Treatment should be initiated when the clinical signs of hypothyroidism and laboratory findings of overt hypothyroidism are evident. There is no reason to avoid prescribing generic formulations, and moving between LT4 brands is not recommended in healthy individuals.[19] In cases of overt hypothyroidism, the recommended daily dosage is 1.5-1.8 ×g per kg of body weight.[19, 33, 49] For individuals with coronary artery disease, the initial dose is usually 12.5-25.0 ×g per day, and it should be gradually increased based on symptoms and TSH levels. TSH levels should be monitored after 4-12 weeks of medication, every six months thereafter, and annually for stable patients. Dosage adjustments should be made based on laboratory findings, as even modest dosage adjustments can significantly impact serum TSH concentrations in certain individuals (e.g., those with low body weight or those who are elderly). Although some individuals may show low T3 levels despite normal TSH levels, routine T3 measurements should not be used to evaluate therapeutic efficacy.[50]

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HYPERTHYROIDISM

Disorders of thyroid hormone excess

Introduction

Hyperthyroidism is a pathological disorder in which excess thyroid hormone (TH) is synthesized and secreted by the thyroid gland. This condition can be overt or subclinical.[1] Hyperthyroidism denotes disorders involving a hyperactive gland, such as Graves' disease (GD), toxic multinodular goiter (MNG), or toxic adenoma/solitary thyroid nodule (STN), whereas thyrotoxicosis is a clinical syndrome of excess circulating and tissue TH levels.[1,2] GD and MNG are the most common causes of hyperthyroidism, whereas thyroiditis, iodine-induced , drug-induced thyroid dysfunction, and factitious ingestion of excess TH cause thyrotoxicosis.[1] Clinical assessments, laboratory tests, and imaging studies are used to diagnose and determine hyperthyroidism.[2] The treatment goals for hyperthyroidism are to lower TH synthesis and secretion, resolve systemic manifestation and treat precipitating illness.[1] Antithyroid drugs (ATDs), radioactive iodine (RAI) ablation, or thyroid surgery are preferred treatment options for hyperthyroidism.[2] If left untreated, hyperthyroidism leads to complications such as weight loss, osteoporosis, fragility fractures, atrial fibrillation, embolic events, and cardiovascular dysfunction.[3]

Definition

Hyperthyroidism is a hypermetabolic state due to the increased - free serum thyroxine (fT4) and/or free triiodothyronine (fT3) and reduced levels of thyroid stimulating hormone (TSH).[4] Hyperthyroidism can be overt or subclinical. In overt hyperthyroidism, the serum TSH concentration is low and fT4, and/ or fT3 concentrations are raised.[1] Subclinical hyperthyroidism is biochemically defined as low serum TSH levels with the levels of fT4 and fT3 within the normal range.[5] Thyroiditis is a group of conditions causing inflammation of the thyroid gland. It can cause transient hyperthyroidism. The most common cause of thyroiditis is an autoimmune disease. In some cases, thyroiditis causes stored TH to release into the bloodstream resulting in developing symptoms of hyperthyroidism.[6]

Epidemiology

Hyperthyroidism is less common than hypothyroidism. The global prevalence of hyperthyroidism ranges from 0.1 to 1.25% (Table 1). It predominantly affects women, and the female-to-male ratio is 8:1.[7]

Table 1: Prevalence of hyperthyroidism in South Asian countries

Country	Overt Hyperthyroidism	Subclinical hyperthyroidism
India[8]	1.3%	1.6%
Sri Lanka[9]	--	5.1%
Bangladesh[10]	0.4%	0.4%
Pakistan[11]	6.0%	5.0%

Etiology

GD is the most common cause of hyperthyroidism, followed by toxic adenoma and multinodular goitre.[1] GD is a condition characterized by organ-specific autoimmunity, whereby autoantibodies in circulation activate the thyroid-stimulating hormone receptor (TSH-R), resulting in the development of hyperthyroidism and goiter. Specifically, stimulatory TSH-R antibody (TRAb) in circulation bind to TSH-R and increase the production of intracellular cyclic adenosine monophosphate, which consequently triggers the release of TH and promotes thyrocyte growth.[3] GD accounts for a substantial majority of hyperthyroid cases, with an estimated prevalence of 60% to 80%. Typically, the condition affects individuals between the ages of 20 and 50, and the incidence rate among women aged 25 to 42 years can be as high as 4.6 per 1000 over a 12-year period. [12] Elderly patients often exhibit apathetic manifestations of hyperthyroidism compared to the cardiac symptoms prevalent in younger individuals. Classical signs like tremors, anxiety, and palpitations are less common

in older adults (age≥70). Instead, symptoms such as weight loss, apathy, and increased heart rate are frequently observed. This lack of typical symptoms in older adults poses a diagnostic challenge, potentially leading to delayed treatment and unfavorable outcomes.[13-15]

GD-specific signs and symptoms are mentioned in Table 2.

Table 2: Etiology of hyperthyroidism	
Effect of increased thyroid stimulators	
Grave's disease[16]	• Most common cause of hyperthyroidism • Autoimmune disorder • Increased TH synthesis and release
Thyroid nodules or adenomas[1,16-17] ➢ Toxic adenoma- Single overactive nodule ➢ Toxic multinodular goiter- Multiple overactive nodules	• Occurs from TSH receptor gene mutation • Overactive nodule produces more TH • Less common than GD • Prevalence rises with age • High risk in the presence of dietary iodine deficiency
TSH-secreting pituitary adenoma; Pituitary resistance to thyroid hormone[16]	• Inappropriate TSH secretion
Trophoblastic tumours- choriocarcinoma[16-17] Hyperemesis gravidarum	• Excess secretion of serum human chorionic gonadotropin (hCG)- a weak thyroid stimulator. • Hyperthyroidism in molar pregnancy, choriocarcinoma, and hyperemesis gravidarum is transient.
Plummer's disease[4]	• Autonomously functioning thyroid nodules that produce increased amounts of THs causing TSH suppression • Common among women and older subjects
Inflammation and release of stored hormone	
Thyroiditis[1,17]	• Autoimmune destruction of the thyroid gland • Secretion of preformed TH from the inflamed thyroid gland
Iodine-induced hyperthyroidism (Excessive iodine exposure) [1,16,17]	• Jod-Basedow phenomenon, Iodine-induced hyperthyroidism (iodine, iodine-containing drugs, radiographic contrast agents)
Toxic drug effects[1]	• Drug-induced thyroiditis (amiodarone, interferon- α, interleukin-2, lithium, iodide, iodinated contrast agents, immune checkpoint inhibitors, and alemtuzumab)
Extrathyroidal source of hormone	
Excess intake of thyroid hormone[1]	• Excess exogenous TH (iatrogenic or factitious)
Hamburger thyrotoxicosis[1]	• Ingestion of contaminated food
Ectopic hyperthyroidism[16,18]	• Struma ovarii (ectopic thyroid tissue existing as a substantial component of an ovarian tumor) • Excess production of TH from ovarian teratomas
*GD: Graves' disease; TH: thyroid hormone; TSH: thyroid stimulating hormone	

Treatment

- Pharmacotherapy includes medications that reduce the clinical manifestations of hyperthyroidism and decrease the synthesis and release of TH.[19]
- Regardless of the cause of hyperthyroidism, the adrenergic symptoms are controlled by β-blockers, which blocks the peripheral conversion of T4 to T3. [19]

- The treatment choice for hyperthyroidism caused by overproduction of THs depends on the patient's age, symptoms, and comorbidities.[19]
- GD can be treated with ATDs such as methimazole (MMI) and carbimazole (CBZ), propylthiouracil (PTU), or RAI (I-131) ablation of the thyroid gland, or surgical thyroidectomy.[19]

ATDs

ATDs (thionamides) are indicated as first-line treatment for GD, particularly in younger subjects, and for short-term treatment of GD before RAI ablation or thyroidectomy.[19] ATDs inhibit TH synthesis exert their action by inhibiting various intrathyroidal processes, including iodine oxidation or organification, coupling of iodotyrosines, biosynthesis of thyroglobulin, and growth of follicular cells. PTU shows extrathyroidal inhibition of T4/T3 conversion. Thionamides act by inhibiting the iodothyronines coupling, which reduces TH biosynthesis.[3,19]

- The initial dose of MMI is 10–30 mg once daily, and CBZ is 15–40 mg/day depending on the severity of hyperthyroidism. PTU is administered at a dose of 100 mg every 8 h, and divided doses are given throughout the course.[3]
- ATD treatment regimen has two approaches:[3]
  - ✓ Titration method is the most preferred regimen in which the dose of ATD is gradually reduced to maintain a euthyroid state. fT4 and fT3 levels are measured every 3-4 weeks after initiation of the treatment and the dose is titrated accordingly. The daily maintenance doses of ATD in this regimen are 2.5–10 mg of MMI and 50–100 mg of PTU.
  - ✓ Block and replace method is an alternative regimen in which MMI 30 mg daily dose is administered along with levothyroxine supplementation to avoid drug-induced hypothyroidism.
- The recommended monitoring protocol for thyroid function in patients with hyperthyroidism involves evaluating fT4 and fT3 levels approximately 2-6 weeks following initiation of therapy, with adjustments made to the ATD dose as needed based on the severity of thyrotoxicosis. Once euthyroid levels are achieved, the ATD dose can be typically reduced by 30-50%, and biochemical testing should be repeated after 4-6 weeks. After reaching euthyroid levels with the minimal medication dose, clinical and laboratory evaluation can be performed every 2-3 months. For patients receiving long-term MMI (>18 months), this interval can be extended to 6 months.[16]
- Monitoring TRAb levels before stopping ATD is essential to predict the outcome of the treatment. Patients with persistently high TRAb levels at 12–18 months can either continue ATD therapy, or opt for RAI or thyroidectomy [3]
- A drawback of ATD therapy is the high rate of relapse of hyperthyroidism after the drug has been discontinued. Relapse is more frequent in the first year than in subsequent years, particularly in the first 6 months after stopping the drug. Patients at higher risk of recurrence are those with severe hyperthyroidism, large goiter, high T3:T4 ratios, persistently suppressed TSH, and high baseline concentrations of TRAb.[1] All patients should be followed closely for relapse during the first year after treatment and at least annually thereafter.[3]

Radioactive Iodine Ablation:

- RAI ablation is the most common treatment of GD.[19]
- Typically, a mean dose of 10–15 mCi (370–555 MBq) is administered to achieve sufficient activity of RAI and effectively treat GD.[16]

- Prior to RAI treatment, ATD therapy should be discontinued for at least five days, and may need to be resumed three to five days after treatment to maintain thyroid function control.[19]
- Thyroid function should be monitored for 1–2 months after RAI ablation.[1] If the patient is still thyrotoxic 1–2 months after RAI therapy, thyroid function should be monitored every 4–6 weeks until the patient is euthyroid or hypothyroid If the patient is still thyrotoxic after 3 months, the patient needs to undergo second ablation. Levothyroxine replacement should be started as soon as hypothyroidism occurs.[1]
- RAI is contraindicated in patients with active moderate-to-severe or sight-threatening Graves' orbitopathy.[1] Other contraindications, include pregnancy, lactation, patients with thyroid cancer, and inability to comply with radiation safety recommendations. [1,3]
- Pregnancy should be ruled out within 48 hours before RAI ablation and avoided for six months thereafter.[19]

Thyroid surgery:

- Thyroid surgery is the preferred treatment for patients who are not candidates for RAI ablation or ATD therapy, although there is a risk of inadvertent injury to parathyroid glands and recurrent laryngeal nerves. [19]
- This therapy is the primary option for hyperthyroidism patients, those with GD who do not achieve remission with primary ATD therapy, patients with moderate-to-severe Graves' orbitopathy, and for those with refractory cases of amiodarone-induced thyrotoxicosis.[2]
- It is also recommended for hyperthyroid patients who have malignant thyroid nodules, patients who cannot tolerate other forms of therapy, and for pregnant women during the second trimester if hyperthyroidism cannot be controlled with an ATD.[2]
- Clinicians should prescribe ATDs for at least a month to achieve a euthyroid state before surgery. Additionally, patients with hyperthyroidism should receive oral potassium iodide during the week before surgery to decrease TH levels and thyroid vascularity. [1]
- Most patients become hypothyroid after surgery and should be started on levothyroxine doses (1.6 µg/kg per day) once hypothyroid. [16]
- Total thyroidectomy is recommended more since the frequency of successful outcomes is significantly higher than with subtotal thyroidectomy. [1]
- Surgical complications are rare and occur in 1–3% of patients. The most frequent complication is hypocalcemia due to permanent hypoparathyroidism, followed by permanent recurrent laryngeal nerve injury (leading to voice changes or breathing problems), hemorrhage, post-surgical infections, and tracheal injury. The risk of these complications is lower when a thyroidectomy is done by a high-volume thyroid surgeon.[1,2]

Recommendations

β-blockers are recommended for all patients to manage symptomatic thyrotoxicosis, especially recommended for elderly patients and thyrotoxic patients with resting heart rates < 90 beats per minute or comorbid cardiovascular disease. (C/IIa)

Patients with GD should be treated with ATDs, RAI ablation, or surgical thyroidectomy. C/II

MMI should be administered in non-pregnant patients undergoing ATD therapy for Graves' hyperthyroidism. C/II

Monitoring TRAb levels before stopping ATD is essential to predict the outcome of the treatment. C/ II

Patients with persistently high TRAb at 12–18 months should continue treatment with MMI or opt for RAI or thyroidectomy. C/IIb

If a patient with GD becomes hyperthyroid after completing a first course of ATD, definitive treatment with RAI or thyroidectomy is recommended. A/IIa

Follow-up within the first 1–2 months after RAI therapy for GD should include an assessment of free T4, total T3, and TSH. Biochemical monitoring should be continued at 4- to 6-week intervals for 6 months, or until the patient becomes hypothyroid and is stable on thyroid hormone replacement. A/ IIb

The physician should provide written advice concerning radiation safety precautions following treatment. If the precautions cannot be followed, alternative therapy should be selected. A/ IIb

A pregnancy test should be obtained within 48 hours prior to treatment in any woman with childbearing potential who is to be treated with RAI. A/ IIb

Pregnancy and breast feeding constitute absolute contraindications to RAI therapy. C/ I

Conception should be postponed until at least 6 months after RAI in both males and females. C/ I

Patients should be rendered euthyroid prior to the surgical procedure with ATD pretreatment, with or without β-adrenergic blockade. A/ IIb

In rare situations, where achieving euthyroidism in a patient with GD before thyroid surgery is not feasible, or when urgent thyroidectomy is necessary, or if the patient has an allergy to ATDs, the patient should receive appropriate treatment with β-adrenergic blockade, glucocorticoids, and possibly cholestyramine during the immediate preoperative period. The surgeon and anesthesiologist should have expertise in managing such cases. A/ IIb

Total thyroidectomy is the preferred procedure, and skilled surgeons with high annual volumes of thyroidectomies should perform the surgery.

Clinical features

Clinical features vary depending on patient's age and sex, comorbidities, duration of the disease, and cause. Older patients present with fewer and less pronounced symptoms than younger patients (Table 3).[1]

Table 3: Common signs and symptoms[17-18]

Most hyperthyroid patient present with one or more of the following symptoms

- Weight loss in spite of a normal or increased appetite
- Proximal myopathy
- Hyperhidrosis
- Heat intolerance
- Tachycardia, arrythmia-atrial fibrillation
- Fatigue
- Anxiety, irritability, insomnia, mood swings
- Fine tremors
- Poor concentration
- Dyspnea and shortness of breath

➢ Periodic paralysis Goitre	
GD specific signs and symptoms	
Hyperthyroidism[16]	Most of the symptoms are similar to common hyperthyroid symptoms, such as tachycardia, tremors, weight loss, muscle weakness, heat tolerance and neuropsychiatric problems.
Thyroid eye disease[1,17]	Early symptoms: Red or inflamed eyes, gritty sensation, photophobia, increased lacrimation, increased sensitivity, dry eyes, periorbital edema, and exophthalmos Late symptoms: Eye socket (orbital) pain, diminished vision, diplopia and reduced color perception
Skin disease[1,18]	Diffuse non-scarring alopecia, palmoplantar hyperhidrosis, facial flushing, skin pigmentation, pretibial myxedema (Graves' dermopathy), patchy vitiligo, thyroid acropachy, changes in nails such as onycholysis and Plummer's nails.
*TED: Thyroid eye disease	

Diagnosis

TSH, fT3 and fT4, TRAb and TPO antibody tests

- Evaluating the thyroid hormone levels including serum TSH, fT4, and fT3 confirms the diagnosis of hyperthyroidism. Measuring serum TSH is the most preferred thyroid function test due to its high sensitivity and specificity to diagnose thyroid disorders. Sometimes all these 3 tests are conducted simultaneously for efficient diagnosis, however, f T4 and fT3 concentrations should be measured to distinguish between subclinical and overt hyperthyroidism.[16,18-19]
- Antibody tests include measuring the serum levels of thyroid peroxidase (TPO) antibodies and TRAb are preferred to distinguish GD from other causes of hyperthyroidism in patients who lack specific signs and symptoms of GD and have a contraindication to radioactive iodine uptake and scan. TRAb is directly involved in the pathogenesis of autoimmune thyroid disorder, therefore, measuring TRAb is essential.[19]
- TRAb is a valuable tool in diagnosing and managing GD and related conditions. The indications for measuring TSH receptor antibodies (TRAb) are:[20]
  - Differential Diagnosis: TRAb measurement is valuable in the initial workup of hyperthyroidism to distinguish GD from other causes of hyperthyroidism, such as subacute painless thyroiditis or drug-induced thyrotoxicosis. It helps confirm GD as the cause of hyperthyroidism.
  - Prognostic Use in GD: TRAb can be used to assess the risk of relapse in GD patients who have achieved euthyroid status while on antithyroid drug treatment. It helps in identifying patients at risk of relapse and guides treatment decisions, such as the continuation of medication or considering definitive treatments like radioiodine therapy.
  - Pregnancy in GD Patients: TRAb measurement is essential during pregnancy in women with GD to assess the risk of fetal and neonatal thyrotoxicosis. High levels of TRAb in pregnant women can lead to fetal thyrotoxicosis, which requires careful monitoring and intervention to protect both the mother and fetus.
  - Confirmation of Graves' Ophthalmopathy: TRAb can confirm the diagnosis of GO, especially in patients with euthyroid GO. Positive TRAb results in these patients provide evidence of the autoimmune nature of the condition and its association with GD.
- Thyroid peroxidase (TPO) antibody test confirms the presence of autoimmune thyroid dysfunction and is also an early predictive marker of thyroid disease.[2]

Imaging

In diagnosing Graves' disease (GD), various imaging techniques can be employed, including:[3]

1. **Thyroid Ultrasound (US):** Thyroid ultrasound is a noninvasive, rapid, and accurate tool commonly used in the initial work-up of GD patients. It aids in the diagnosis, helps determine the underlying cause of thyrotoxicosis, and detects concomitant thyroid nodules. GD is often characterized by diffuse thyroid enlargement and hypoechogenicity, which can be assessed using US and conventional grey scale analysis.
2. **Color-Flow or Power Doppler Examination:** This imaging technique characterizes vascular patterns and quantifies thyroid vascularity. In untreated GD, thyroid vascularity is significantly increased and typically shows a pulsatile pattern known as "thyroid inferno." It involves multiple small areas of increased intrathyroidal flow seen diffusely throughout the gland. Accurate measurement of thyroid artery flow velocity and peak systolic velocity (PSV) is possible through this technique.
3. **Thyroid Scintigraphy:** While less commonly used than ultrasound, thyroid scintigraphy can be employed in some cases, particularly in assessing patients before radioactive iodine (RAI) treatment. It may be useful, especially when coexistent multinodular goiter is a concern.
4. **CT Scan, MRI, or PET-CT:** Typically, there is no indication for these advanced imaging techniques in the routine diagnosis of GD. They are reserved for specific clinical situations where more detailed information about thyroid and surrounding structures is necessary.

Further investigations

- ESR and CRP are used to aid the diagnosis of thyroiditis.
- ECG changes are seen in hyperthyroidism.[22] It can lead to atrial arrhythmias such as sinus tachycardia, atrial flutter, atrial fibrillation, and prolonged and shortened QT interval.[23]

Indications to screen for hyperthyroidism

- Individuals with goiter, type 1 diabetes, osteoporosis, subfertility, other autoimmune diseases, and a family history of thyroid disease.[2]
- Certain drugs induce hyperthyroidism.[2]
- Screening for hyperthyroidism is recommended for patients with medical conditions that may be caused or aggravated by thyrotoxicosis including[2]:
    - ✓ Osteoporosis
    - ✓ atrial fibrillation
    - ✓ supraventricular tachycardia
    - ✓ heart failure

Recommendation

- The initial diagnostic workup for hyperthyroidism includes measuring TSH, free T4, and total T3 levels to determine the presence and severity of the condition. C/II
- TRAb testing is a sensitive and specific tool for rapid and accurate diagnosis or differential diagnosis of hyperthyroidism. A/I
- Ultrasound (conventional grey scale analysis and color-flow or power Doppler) is recommended as the imaging procedure to support the diagnosis of GD. A/I
- Radioactive iodine uptake and a scan of the thyroid gland determines the cause of hyperthyroidism. C/II
- Multiple tests are not required in the initial evaluation of a patient suspected of thyroid disease. C/II
- Serum TSH test is the preferred initial test, and if the result is abnormal, follow-up with additional evaluation or treatment depending on the findings. C/II
- Thyroid ultrasound should not be routinely advised in patients with abnormal thyroid function tests if there is no palpable abnormality of the thyroid gland. C/II

Thyroid eye disease (TED)

TED is an autoimmune inflammatory condition that affects ocular and orbital tissues in association with thyroid disease, with approximately 90% of cases occurring in hyperthyroid patients.[23-24] TED is a rare disease with an incidence rate of approximately 19 in 100,000 people per year.[23] The overall incidence in the population is low. [25] Even mild cases of TED can negatively impact a patient's quality of life, as it can cause diplopia, ocular hypertension, optic nerve damage, and glaucoma.[26] While TED is more common in younger females, studies have posited that males and advancing age are at a higher risk of severe disease. Asian countries showed the highest prevalence of TED (44%, CI: 0.32 to 0.56) followed by Europe (38%, CI: 0.31 to 0.46) and North America (27%, CI: 0.06 to 0.56).[26] TED affects women 5 times more compared with men due to the higher incidence of GD in women. Patients aged above 50 years diagnosed with TED have a worse prognosis overall.[23]

Risk factors associated with TED include genetic, environmental (smoking- most consistent risk factor related to the progress of the disease; stress), and immune factors.[23] Other risk factors include thyroid dysfunction, high serum level of thyrotropin receptor antibodies, RAI treatment, and hypercholesterolemia.[16]

TED signs and symptoms are discussed in Table 3.

Diagnosis

The diagnosis of the disease can be made clinically based on the typical clinical features, as well as the restrictive nature of the disease and associated systemic thyroid disease. While not definitive, laboratory tests such as TH levels, thyroid-stimulating immunoglobulins (TSI), anti-thyroid antibodies (such as anti-thyroid peroxidase antibodies, anti-thyroglobulin antibodies), can support the diagnosis. Ultrasonography using A-scan and B-scan transocular echograms can be utilized to visualize orbital structures and determine recti muscle (extraocular muscles) enlargement, which is cost-effective, radiation-free, and takes a relatively short time. Imaging techniques such as computed tomography (CT) scans can differentiate normal structures from abnormal structures of different tissue density, demonstrating enlargement of the bellies and sparing of the tendons. Magnetic resonance

imaging (MRI) can identify fusiform rectus enlargement and orbital fat expansion and aid in assessing water content in the muscles and other soft tissues, which may correlate with active inflammation. These imaging techniques can also help in planning for surgical intervention if required (Table 4).[23]

Table 4: Laboratory tests and imaging techniques for diagnosing TED	
Laboratory Tests	Imaging Techniques
- TH levels	- Ultrasonography using A-scan and B-scan transocular echograms
- Thyroid-stimulating immunoglobulins (TSI)	- Computed tomography (CT) scans
- Anti-thyroid antibodies	- Magnetic resonance imaging (MRI)

TED is evaluated based on the activity and severity of the disease. Activity shows the grade of active inflammation and defines the progression of the disease. The severity indicates the spectrum of functional deficits.[27]

Clinical activity score (CAS): Essential for clinical assessment and grading of TED

CAS grading system distinguishes the active and stable phases of the disease and grades the classic signs of inflammation. Each CAS score item is given one point and sum of these points is the CAS (range 0–10) (Table 5).[23]

Table 5: CAS to evaluate thyroid eye disease.[23]	
Score	For initial CAS score items 1-7
1	• Spontaneous orbital pain
2	• Gaze evoked orbital pain
3	• Eyelid swelling that is considered to be due to active GO
4	• Eyelid erythema
5	• Conjunctival redness considered due to active GO
6	• Chemosis
7	• Inflammation of caruncle or plica
Score	Follow-up after 1-3 months score item including 8-10
8	• Increase of >2mm proptosis
9	• Decrease in ocular excursion in any one direction of >8 degrees
10	• Decrease of acuity equivalent to 1 Snellen line
*one point is added for the pr4esence of each of the parameters assessed and the sum of all points define the clinical activity. #CAS score >3/7 at first examination depicts active ophthalmopathy CAS score >4/10 at successive examination depicts active ophthalmopathy; GO: Graves' orbitopathy	

NOSPECS classification

It grades only the clinical severity of TED and not on the activity of the disease (Table 6).[24]

Table 6: NO-SPECS ((No signs or symptoms; Only signs or symptoms; Soft tissue involvement; Proptosis; Extraocular muscle involvement; Corneal Involvement; Sight loss) classification[28]

Class	Abbreviation	Description	Detailed Description
O	N	No signs or symptoms	No complaints, No findings in physical examination (PE)
1	O	Only signs, no symptoms	No complains, PE: Eyelid retraction Stare
2	S	Soft tissue involvement	Swelling of eyelids Chemosis Photophobia Grittiness
3	P	Proptosis	Exophtalmus
4	E	Extraocular muscle involvement	Restricted eyeball mobility (often diplopia)
5	C	Corneal involvement	Keratitis, Corneal Ulcer
6	S	Sight loss	Decreased visual acuity, impaired color of vision (optic nerve involvement)

VISA classification

VISA include assessing for 4 severity parameters, including Vision, Inflammation, Strabismus (motility restriction), and Appearance, a maximum score of 20 is used to grade the severity of the disease. Each of the four parameters has further divisions to assess the activity of the disease accurately.[24]

EUGOGO Classification

This classification assesses both disease activity and severity. Activity is based on four measures of inflammation, pain, redness, swelling, and impaired function, and function is graded with decreasing monocular motion and diminishing visual acuity. The classification system also has developed an image atlas for accurate grading. Additionally, the EUGOGO grading system does well in differentiating management categories (Table 7).[24]

Table 7: Severity classification in TED according to EUGOGO.[24]	
Sight threatening TED	• Patients with dysthyroid optic neuropathy and / or corneal breakdown. • This category needs immediate intervention
Moderate-to-severe TED	• Patients usually have lid retraction ≥ 2mm, moderate or severe soft tissue involvement, exophthalmos ≥ 3mm above normal for race and gender and inconstant or constant diplopia. • Patients usually have any one or more of the above symptoms. • The features of the patient have sufficient impact on daily life to justify the risk of immunosuppressive or surgical treatment.
Mild TED	• Patients usually have lid retraction < 2mm, mild soft tissue involvement, exophthalmos < 3mm above normal for race and gender and transient or no diplopia. • Patients usually have only one or more of the above symptoms. • The features of the patient have minor impact on daily life insufficient to justify the risk of immunosuppressive or surgical treatment.

Table 8: Signs and symptoms of STN and MNG[29]	
Symptoms of thyrotoxicosis • Nervousness • Fatigue • Sweating • Heat intolerance • Difficulty concentrating • Tremor • Palpitation • Weight loss • Loose stools • Menstrual irregularities	Signs of thyrotoxicosis • Hyperactivity • Irritability • Tachycardia/arrhythmia • Systolic hypertension • Warm, moist skin • Tremor • Hyperreflexia • Muscle weakness • Oedema Shortness of breath
Compression symptoms in case of large STN or MNG • Increase in collar size • Neck swelling • Difficulty swallowing • Shortness of breath • Pemberton's sign	

Diagnosis

The diagnosis of STN and MNG is based on clinical examination, thyroid function tests, thyroid ultrasound, and scintiscan. Thyroid gland (neck examination) examination will reveal a nodule on palpation. Thyroid function tests and a complete medical history assessment of the patient are necessary. An ultrasound scan of the neck should be carried out to assess the thyroid nodule. Radioactive iodine (RAI) scan is important to differentiate between hot nodules and cold nodules. Imaging techniques such as CT scanning or MRI may be required to evaluate any thyroid enlargement and its impact on the neighboring structures.[29] Fine needle aspiration cytology is also an important investigation, especially in patients with a high risk of malignancy.[30]

Treatment

Regular monitoring with repeat ultrasonography is usually recommended for some asymptomatic patients with small thyroid adenomas and no malignancy detected by fine needle aspiration. If the nodule expands in size during subsequent exams or if other suspicious signs are identified during a radiologic evaluation using an ultrasound, the FNA might need to be repeated.

Patients with benign thyroid adenomas or those with minimally invasive thyroid cancer can undergo thyroid lobectomy and isthmusectomy as an appropriate surgical treatment. If histological examination does not reveal any signs of malignancy, no additional intervention is necessary. These patients should simply have their thyroid hormone levels regularly monitored.

Patients with solitary toxic nodules can be managed with anti-thyroid drugs, iodine-131 therapy, or thyroidectomy. Surgery offers relief from symptoms, immediate resolution of hyperthyroidism, and avoids radiation exposure to healthy thyroid tissue. Ethanol injections are an option, but their long-term effectiveness is uncertain. Monitoring thyroid function post RAI is necessary. It is recommended to measure thyroid function test at 4–6 weeks intervals for 6–12 months until hypothyroidism occurs or stable euthyroidism is attained.[29]

Toxic multinodular goiter (MNG)

Toxic multinodular goiter (MNG), also known as Plummer disease, contains multiple autonomously functioning nodules. These nodules function independently of TSH and are benign. It is the second most common etiology for

Treatment

The treatment of inactive moderate to severe TED requires the use of rehabilitative surgical therapies such as orbital decompression, strabismus surgery or eyelid surgery. Hence, it is important to be able to differentiate between the two phases of TED for effective management. This can be done through the use of the grading systems such as CAS, EUGOGO, NOSPEC classification guidelines or VISA scoring guidelines.

Conservative management involves smoking cessation and maintaining euthyroid status are essential to prevent further exacerbation and reduce the duration of active disease. To address corneal exposure, various approaches can be tried, such as lubricants, taping, and protective shields. If necessary, tarsorrhaphy can be considered. For diplopia, treatment options include using Fresnel prisms or occlusion therapy. Lifestyle modifications, such as reducing sodium intake to minimize water retention and tissue edema and sleeping with the head of the bed elevated to reduce orbital edema, can also be beneficial. Oral nonsteroidal anti-inflammatory drugs (NSAIDs) can alleviate periocular pain. Furthermore, selenium supplementation has demonstrated significant benefits in patients with mild, non-inflammatory orbitopathy.[27]

Medical management:

A cumulative dose of 4.5 g of intravenous (IV) methylprednisolone in 12 weekly infusions is the optimal treatment regimen for TED.[23]

Second-line treatments for moderate-to-severe and active TED include[23]

- A second course of IV methylprednisolone (7.5 g) after careful ophthalmic and biochemical evaluation.
- Oral prednisone/prednisolone combined with either cyclosporine or azathioprine.
- Orbital radiotherapy combined with oral or IV glucocorticoids, teprotumumab; rituximab and tocilizumab.

Sight-threatening TED is treated with several high single doses of IV methylprednisolone per week and, if unresponsive, with urgent orbital decompression. Rehabilitative surgery (orbital decompression, squint, and eyelid surgery) is indicated for inactive residual TED manifestations.[27]

Toxic adenoma/Solitary thyroid nodule

Toxic thyroid adenoma/solitary thyroid nodule (STN) is an autonomously functioning thyroid nodules. These are benign monoclonal tumors that can develop and produce T4 and T3 autonomously. It frequently affects women between the ages of 30 and 60, with a female: male ratio varying from 6:1 to 15:1. STN accounts for approximately 2% of all hyperthyroidism.[29] Iodine deficiency is the most common cause of TA. Also, rare genetic mutations are strongly associated with the development of TA.[30]

Clinical signs

Patients typically present with signs and symptoms of thyrotoxicosis, including nervousness, fatigue, heat intolerance, hyperactivity, irritability, tachycardia/ arrhythmia, hyperreflexia, and systolic hypertension. Other symptoms in the case of large STN include increased collar size, neck swelling, shortness of breath, and Pembertons' sign (Table 8)[29]

hyperthyroidism. MNG is prevalent in the age group of 50 years and above, both in males and females. In elderly individuals and areas of endemic iodine deficiency, MNG is the most common cause of hyperthyroidism. A simple and diffuse goiter develops into a multinodular goiter. Chronic intermittent stimuli lead to diffuse hyperplasia of thyroid and formation of autonomously functioning nodules or multiple nodules on the gland. Heat intolerance, palpitation, tremor and weight loss are some of the common clinical manifestations of MNG. [31]

Diagnosis

Diagnostic techniques include laboratory studies in which serum TSH, T3 and T4 are evaluated. Antithyroid peroxidase (anti-TPO), antithyroglobulin antibodies and thyroid stimulating immunoglobulin are other laboratory examinations. Imaging techniques such as ultrasonography, thyroid scintigraphy, FNAC, CT and MRI are preferred diagnostic techniques. [31]

Treatment[31]

- Thyroid surgery is the primary treatment for MNG which provides rapid resolution along with low morbidity and mortality. Total, near total, or subtotal thyroid surgery may be done based on the disease state.
- Thyroid surgery may lead to complications, including unilateral or bilateral vocal cord paralysis, hypoparathyroidism, significant post-operative bleeding or infection, and tracheostomy.
- RAI ablation is a safe and effective treatment, but it does not entirely resolve the disease, and the results are delayed. RAI treatment results in complications such as secondary cancers, hypothyroidism, mild thyrotoxic symptoms, tracheal compression, exacerbation of atrial fibrillation, and thyroid storm.
- ATD can be used during the waiting period until RAI treatment or surgical preparations.
- Percutaneous ethanol ablation is a minimally invasive procedure to treat hyperfunctioning nodules. Ethanol ablation is favorable for patients who are unfit for undergoing surgery. Ethanol ablation shows good short-term results, but the long-term results are unsatisfactory.

Recommendation

- In patients with STN or MNG, sufficient activity of RAI should be administered in a single application to alleviate hyperthyroidism. C/I
- Follow-up within the first 1–2 months after RAI therapy for MNG or STN should include an assessment of thyroid function test. C/I
- In STN or MNG, biochemical monitoring should be performed at 4- to 6-week intervals for 6 months, or until the patient becomes hypothyroid and is stable on thyroid hormone replacement. C/I
- Retreatment with RAI is suggested if hyperthyroidism persists beyond 6 months following RAI therapy for TMNG or TA. C/II a
- STN or MNG patients with overt hyperthyroidism should be rendered euthyroid before the surgery using MMI pretreatment, with or without β-adrenergic blockade. C/ IIa
- Long-term MMI treatment of TMNG or STN might be indicated in some elderly or otherwise ill patients with limited life expectancy, in patients who are not good candidates for surgery or ablative therapy, and in patients who prefer this option. C/IIb

Thyroiditis

Thyroiditis is a condition of inflamed thyroid gland encompassing several clinical disorders. Patients may present with a goiter, features of hyperthyroidism or hypothyroidism depending on the phase of thyroiditis.[33] Some types of thyroiditis can cause TH leak from the thyroid gland resulting in the development of hyperthyroidism, whereas the other types of thyroiditis can cause hypothyroidism.[32]

Etiology[32]

Thyroiditis can be caused due to autoimmune disease, infections, drugs, or fibrosis and it is classified into 3 groups based on the etiologies.

Acute thyroiditis is caused by bacterial infection of the gland.
Subacute (granulomatous) thyroiditis is caused by viral infection of the gland.
Chronic thyroiditis is caused by autoimmune, or iatrogenic and drug-induced diseases.

Thyroiditis leads to hyperthyroidism or hypothyroidism and most types of thyroiditis has 3 phases including the thyrotoxic, hypothyroid and euthyroid phase. Various types of thyroiditis are discussed below.

Acute thyroiditis

Acute bacterial suppurative thyroiditis is an uncommon but severe infection that may progress to thyroid abscess.[33] It accounts for < 1% of thyroid diseases. Mostly children (92%) are affected by this condition. Acute suppurative thyroiditis occurs due to hematogenous or lymphatic spread or may be iatrogenic after fine needle aspiration biopsy. Immunocompromised subjects are more susceptible to this condition. If this condition is left untreated it can be life threatening, resulting in 12% or higher mortality.[34]

Clinical presentation

Patients may present with fever, neck pain, hoarseness, sore throat and, dysphagia.[34]

Diagnosis

Ultrasound of the thyroid gland would adequately demonstrate any lesions of the thyroid as well as adjacent lymphadenopathy.[34]

Treatment

Parenteral antibiotics is the mainstay of the treatment and surgical drainage is recommended if the abscess does not resolve.[33-34]

Subacute thyroiditis

Postpartum thyroiditis

Postpartum thyroiditis (PPT) is an autoimmune disorder that occurs within one year of parturition, miscarriage, or medical abortion in women without a history of thyroid disease prior to pregnancy. PPT is prevalent in 8% of pregnancies. The prevalence of PPT is high in patients with type 1 diabetes, positive anti TPOAb, history of PPT in the previous pregnancy, and a positive family history. PPT may occasionally result in permanent hypothyroidism. Recurrence rate risk of PPT in subsequent pregnancies may be as high as 42.4%.[35-36]

Clinical presentation

Symptoms of hyperthyroidism and hypothyroidism are usually mild.[36]

Diagnosis

fT3, fT4 and TSH would help in establishing the phase of PPT. RAI uptake though of great value should not be performed if the mother is lactating. [36]

Treatment

Palpitations, anxiety, and tremors should be treated with β-blockers and monitored closely. If the TSH greater than 10 mIU/L with/without symptoms of hypothyroidism short-term LT4 treatment is required. Long-term monitoring for thyroid functions is required till patient is euthyroid.[36]

De Quervain thyroiditis

De Quervain thyroiditis is a form of self-limited subacute thyroiditis usually preceded by an upper respiratory tract viral infection. It predominantly affects women between the ages of 25 to 35 years.[35,37]

Clinical presentation

Anterior neck pain is the cardinal feature of subacute thyroiditis. Dysphagia, increased sweating, tremor, and weight loss are some of the common symptoms. Thyroid gland may be diffusely enlarged.[37]

Diagnosis

CBC, ESR, fT3, fT4, TSH, thyroid antibodies, thyroid ultrasonography and thyroid scan would help in clinching the diagnosis.[35, 37]

Treatment

First line treatment is pain relief which is achieved by administration of acetylsalicylic acid or nonsteroidal anti-inflammatory drugs-. Corticosteroids for 4-8 weeks are an important part of armamentarium. Palpitations, anxiety, and tremors should be treated with β-blockers and monitored closely.

If the TSH is greater than 10 mIU/L with/without symptoms of hypothyroidism short-term LT4 treatment is required. Long-term monitoring for thyroid functions is required till patient is euthyroid.[35, 37]

Silent thyroiditis

Silent thyroiditis, also known as painless thyroiditis, is a common cause of transient hyperthyroidism characterized by recent onset of symptoms in a patient with a normal to modestly enlarged and firm thyroid gland.[39] It accounts to approximately 0.5 to 5% of hyperthyroidism. In silent thyroiditis, patients experience an initial hyperthyroid phase, followed successively by hypothyroid and recovery phases. The hyperthyroid phase lasts three to four months whereas the hypothyroid phase may last from one to eight months. Recovery usually occurs within six months but may extend upto 21 months.[38] Silent thyroiditis is less likely to result in permanent hypothyroidism (up to 11% of patients), and recurrence is less common.[35]

Diagnosis

Apart from fT3, fT4, TSH, and anti-TPOAb a markedly suppressed RAI uptake would help in establishing the diagnosis. FNAb shows prominent lymphocytic infiltration.[38]

Treatment

Palpitations, anxiety, and tremors should be treated with β-blockers and properly monitored. If the TSH is greater than 10 mIU/L with or without hypothyroidism symptoms, short-term LT4 medication is indicated. Long-term thyroid function monitoring is essential until the patient achieves euthyroid status. β-blockers are used to control thyrotoxic symptoms. For the patient who experiences recurrent episodes of silent thyroiditis with hyperthyroidism, RAI ablative therapy during a recovery phase is recommended. Short-term levothyroxine treatment is recommended to patients who experience a prolonged period of hypothyroid phase before recovery.[37]

Chronic thyroiditis

Drug-induced thyroiditis

Drug-induced thyroiditis is caused by intake of medicines such as amiodarone, interferon (IFN)-a, interleukin-2, tyrosine kinase inhibitors, and lithium which leads to thyroid cell damage. This condition can lead to thyrotoxicosis or hypothyroidism and discontinuing the use of such medications can decrease progression and/or may result in resolution of the condition.[39] Patients who are administering medications that cause thyrotoxicosis should be monitored clinically and biochemically at 6-month intervals for identifying the development of thyroid dysfunction.[40] Drugs inducing thyroiditis and their mechanisms are presented in Table 9.

Table 9: Summary of drug-induced thyroiditis[41]

Drug	Mechanism	Clinical syndrome	Treatment
Amiodarone	Type 1 thyroiditis - increased synthesis in patients with pre-existing goiter	Thyrotoxicosis	Antithyroid medication
	Type 2 thyroiditis - destructive thyroiditis with release of excessive thyroid hormones	Thyrotoxicosis	Prednisolone
Lithium	Impairs iodine uptake, inhibits synthesis and release of thyroid hormones; suspected of causing thyrotoxicosis through direct toxic effect	Hypothyroidism and goitre formation	Lithium
Tyrosine kinase inhibitors	• Hypothyroidism resulting from its antiangiogenic effect • Peripheral inactivation of thyroid hormones	Hypothyroidism, may be preceded by transient thyrotoxic phase	Thyroxine for new hypothyroidism Increase thyroxine dose in cases of previously stable hypothyroidism
Interleukin-2 Alpha interferon Alemtuzumab	• Immune related; de novo antibody production or exacerbation of underlying AITD • IL-2-related hypothyroidism correlated with a favorable response to treatment	• Transient hypothyroidism (35%) • Permanent hypothyroidism (9%) • Hyperthyroidism (GD or destructive thyroiditis)	Thyroxine for hypothyroidism Antithyroid agent for GD
Immune checkpoint inhibitors	• Immune-related thyroiditis; rarely, GD • Immune-related hypophysitis may cause central hypothyroidism. • Overt thyrotoxicosis is associated with high rates of cancer survival	Destructive thyroiditis with transient thyrotoxicosis followed by hypothyroidism GD-persistent hyperthyroidism (less common)	• Beta blockers to manage symptoms in transient thyroiditis. • Thyroxine to manage hypothyroidism. • For combined adrenal and thyroid dysfunction due to hypophysitis, manage with corticosteroid replacement before levothyroxine replacement to avoid acute adrenal crisis

Clinical presentation

The signs and symptoms depend on the clinical state and are usually mild.[39]

Diagnosis

Serum TSH, fT3 and fT4, anti-TPOAb, , and RAI uptake tests are performed to diagnose the condition. [39]

Treatment

The treatment will depend on the thyroid function status (Hypo or hyper). Corticosteroids may also be required in certain cases.[39]

Hashimoto's thyroiditis

Hashimoto's thyroiditis is an autoimmune condition characterized by lymphocytic infiltration, fibrotic transformation of the thyroid gland, and elevated serum autoimmune antibody levels.[8,33] It is the most prevalent form of thyroiditis and a frequent cause of hypothyroidism in regions with iodine abundance. The global prevalence of Hashimoto's thyroiditis has increased, and women are at approximately four times higher risk than men. The prevalence varies by region and socioeconomic level, ranging from 4.8–25.8% in women and 0.9–7.9% in men.[42]

Clinical Presentation

The symptoms depend on the degree of thyroid dysfunction. Patients typically present with nontender goiter, hypothyroidism and an elevated TPO antibody level. Sometimes Hashimoto's thyroiditis presents without a goiter (atrophic form) representing an extensive thyroid fibrosis which is likely to result in overt hypothyroidism.[32,35]

Who are at risk? [32,35]

- Patients with a family or personal history of autoimmune thyroid disease
- Female patients
- Patients with type 1 diabetes mellitus, Turner syndrome, Addison disease, and untreated hepatitis C

Diagnosis

Thyroid examination shows a firm, bumpy gland with symmetric enlargement. Thyroid peroxidase antibody and thyroglobulin tests are preferred laboratory examination. Other thyroid function tests such as serum TSH, free T4 are also performed. [32,35]

Treatment

Patients with hypothyroidism is treated with levothyroxine at a starting dosage of 1.6 mcg per kg per day which can be subsequently increased every 10 to 12 weeks to achieve a goal TSH level of 1 to 3 mIU/L.[35]

Table 10 summarizes the different types of thyroiditis.

Table 10: Types of thyroiditis

Aspect	Acute Bacterial Suppurative Thyroiditis	Subacute thyroiditis			Chronic thyroiditis	
		DeQuervain's) Thyroiditis	Postpartum Thyroiditis	Silent Thyroiditis	Drug-Induced	Hashimoto's Thyroiditis
Prevalence	< 1%	Uncommon	8% of pregnancies	0.5-5% of hyperthyroidism cases	Varies depending on the medication taken	Most prevalent form of thyroiditis

Population Affected	Mostly children, immunocompromised individuals	Predominantly women (25-35 years)	Women after childbirth/miscarriage	Patients with recent onset symptoms	Individuals taking specific medications	Women, individuals with autoimmune conditions
Etiology	Bacterial infection (hematogenous, lymphatic, iatrogenic)	Viral upper respiratory infection	Autoimmune disorder	Recent onset symptoms in a normal/modestly enlarged thyroid gland	Intake of medications such as amiodarone, interferon, lithium, etc.	Autoimmune condition
Clinical Symptoms	Fever, neck pain, hoarseness, dysphagia	Anterior neck pain, sweating, tremor	Mild hyper/hypothyroidism symptoms	Transient hyperthyroidism followed by hypothyroidism	Variable symptoms depending on hypo/hyperthyroidism	Nontender goiter, hypothyroidism, elevated TPO antibodies
Diagnosis	Ultrasound, CBC, thyroid antibodies	CBC, thyroid hormones, antibodies, ultrasound	Thyroid hormones, RAI uptake tests	fT3, fT4, TSH, anti-TPOAb, markedly suppressed RAI uptake	Serum TSH, fT3, fT4, anti-TPOAb, RAI uptake tests, thyroid ultrasonography	Thyroid examination, TPO antibodies, thyroid function tests
Treatment	Antibiotics, drainage if abscess persists	Pain relief, corticosteroids, β-blockers if needed	β-blockers, LT4 if TSH > 10 mIU/L	β-blockers, LT4 if TSH > 10 mIU/L	Adjust or discontinue medication, corticosteroids may be required	Levothyroxine for hypothyroidism, regular monitoring
Risk Factors	Immunocompromised state	Not specified	Previous PPT, diabetes, family history	Not specified	Use of medications like amiodarone, interferon, lithium, etc.	Family/personal history of autoimmune thyroid disease, female gender, certain autoimmune conditions
Long-term Effects	Potentially life-threatening, >12%mortality	Self-limited, recovery within months	May lead to permanent hypothyroidism, recurrence in pregnancies	May result in permanent hypothyroidism	Depends on the specific drug, may resolve upon discontinuation	Hypothyroidism, lifelong levothyroxine therapy

Recommendation

Thyroditis may be acute, subacute or chronic.

Acute thyroiditis should be treated with parenteral antibiotics and surgical drainage. C/ IIa

Patients with subacute thyroiditis should be started on high-dose acetylsalicylic acid or nonsteroidal anti-inflammatory drugs as first-line therapy. C/II b

Corticosteroid therapy for subacute thyroiditis should be initiated in patients with severe neck pain or minimal response to acetylsalicylic acid or nonsteroidal anti-inflammatory drugs after four days. C/ IIb

Postpartum thyroiditis with TSH > 10 mIU/L, with or without hypothyroid symptoms, requires short-term LT4 treatment. C/IIa

β-adrenergic-blockers should be used to control symptoms in patients with symptomatic thyrotoxicosis due to silent thyroiditis. C/ IIa

Patients taking medications that cause thyrotoxicosis, including interferon (IFN)-a, interleukin-2, tyrosine kinase inhibitors, and lithium, should be monitored clinically and biochemically at 6-month intervals for the development of thyroid dysfunction. C/ IIa

Hyperthyroidism in the elderly population

Etiology

Etiology is the same across all age groups.

Treatment

The treatment choice depends on the etiology of hyperthyroidism.[43]

- Anti-thyroid drugs[43]:
  - ✓ PTU may be initiated at 150 to 300 mg/day orally in divided doses every 8 hourly (dosage to be based on serum TSH levels).
  - ✓ CBZ should be initiated at 15 to 40 mg/day as a single daily dose.
- RAI is the treatment of choice for elderly patients with hyperthyroidism. MMI should be administered before RAI and discontinued approximately five days prior to therapy. MMI should be given for 1 or 2 weeks after radioiodine administration in order to avoid interference with radioiodine recycling and a possible reduction in the efficacy of the radioiodine. [43-44]
- Long-term low-dose ATD (MMI 2.5–5 mg daily) is an effective and well-tolerated treatment, especially in absence of RAI and/or contraindication to thyroidectomy.[3]
- β-blockers are useful adjuncts to ATDs to manage sympathetic symptoms of hyperthyroidism. β-blockers can also be administered after radioiodine administration to prevent cardiac side effects.[43]
- Anticoagulation with coumarin derivatives such as warfarin should be considered in elderly subjects with thyrotoxicosis complicated by atrial fibrillation.[43]
- Salicylates are effective for relief of local pain and tenderness in cases of subacute thyroiditis.[43]
- Surgical thyroidectomy is least preferred in elderly population. However, it is the treatment of choice for MNG.[43]

Recommendation

Elderly patients with atrial fibrillation, cardiac failure, or cardiac ischemic symptoms due to hyperthyroidism should undergo definitive therapy, usually RAI. A/ IIa

Long-term ATD should be considered as a satisfactory treatment for older individuals with mild GD. C/ IIb

Subclinical hyperthyroidism

Introduction

- Subclinical hyperthyroidism is characterized by a low or undetectable serum TSH level, with normal total or free T4 and total or free T3 levels.[45]
- Subclinical hyperthyroidism is subdivided into two categories on basis of serum level of TSH
  - ✓ Grade 1 - TSH level is low but detectable (0.1 - 0.4 mIU/L)

- ✓ Grade 2- TSH level <0.1 mIU/L

- Subclinical hyperthyroidism is less common affecting 1% to 2% of the general population. It is more common in women, elderly and iodine-deficient areas.[45-46]

Etiology and complications

Etiology of subclinical and overt hyperthyroidism are the same. In elderly patients, MNG is probably the most common cause of subclinical hyperthyroidism. There is a high risk of bone fracture in postmenopausal women, and atrial fibrillation and heart failure in elderly subjects.[47]

When to treat subclinical hyperthyroidism

Table 11 indicates a summary of factors to consider when deciding whether or not to treat a patient with subclinical hyperthyroidism.[16]

Table 11. American Thyroid Association Recommendations for Treating Adults with Subclinical Hyperthyroidism[16]

Factor	TSH < 0.1 Miu per L	TSH 0.1 to 0.4 Miu per L*
Age ≥ 65 years	Treat	Consider treating
Age < 65 years in the asymptomatic patient	Consider treating	Observe
Age < 65 years with comorbidities		
Heart disease	Treat	Consider treating
Hyperthyroid symptoms	Treat	Consider treating
Osteoporosis	Treat	Consider treating
Postmenopausal (no estrogen or bisphosphonate therapy)	Treat	Consider treating

TSH = thyroid-stimulating hormone. *—0.4 Miu per L is the lower limit of the normal range.

Treatment

Treatment of subclinical hyperthyroidism is not different from overt hyperthyroidism.

- Long-term treatment with ATD (over 12 to 18 months) is a sensible first option to radioiodine therapy since the remission index is high in patients with mild disease, especially in young adults. [47]

Recommendation

When TSH is persistently <0.1 mU/L, treatment of subclinical hyperthyroidism is recommended in all individuals ≥ 65 years of age; in patients with cardiac risk factors, heart disease or osteoporosis; in postmenopausal women who are not on estrogens or bisphosphonates; and in individuals with hyperthyroid symptoms. C/I

Subclinical hyperthyroidism treatment should be based on the etiology of the thyroid dysfunction and the treatment principles are same to the overt hyperthyroidism therapy. C/I

Thyrotoxicosis in Pregnancy

Thyrotoxicosis during pregnancy is of clinical concern and if left untreated or inadequately treated can lead to adverse pregnancy outcomes.[48] Approximately 2.4% of pregnancies (0.6% overt and 1.8% subclinical hyperthyroidism) are affected by hyperthyroidism.[49-50] Recognizing and treating overt hyperthyroidism is essential to prevent maternal and fetal complications.[49] GD affects 0.4-1.0% of women in the preconception period and about 0.2% of pregnant women. It is the most frequent cause of overt persistent hyperthyroidism among these women.[51] Ideally, hyperthyroidism is identified prior to conception and therapy is initiated to establish a euthyroid state.[49]

Another most prevalent cause of hyperthyroidism in pregnancy is gestational transient thyrotoxicosis (GTT) which results from the stimulation of the TSH receptor by human chorionic gonadotropin (hCG).[51] The incidence of GTT, transient (hCG)-mediated hyperthyroidism, in the first trimester of pregnancy may be highest in Asian populations and has been estimated at between 1 and 11%.[51]

It is important to distinguish between the two types of hyperthyroidism found in pregnancy since the illness course and treatment choices differ.[50]

- Toxic multinodular goiter and toxic adenoma are two less frequent non-autoimmune causes of hyperthyroidism in pregnancy.[52]
- Some of the lesser frequent causes of thyrotoxicosis in pregnancy include subacute, painful, or painless thyroiditis with the passive release of thyroid hormones from a damaged thyroid gland, whereas several other conditions like a TSH-secreting pituitary adenoma, struma ovarii, functional thyroid cancer metastases, or germline TSH receptor mutations are very rare.[52]

Diagnosis

TSH[53]

- A serum TSH below 0.1 mU/L (in some cases even undetectable) may be present in women by week 11.

Total T4, T3, and free T4 index[53]

- Serum total T4 and T3 levels more than 1.5 times the non-pregnant range should be used to diagnose thyrotoxicosis in 2nd and 3rd trimesters of pregnancy.
- Measurement of the free T4 index (FTI), which adjusts for the presence of binding proteins, has also been proposed as an alternate and perhaps more accurate test for diagnosing hyperthyroidism.

TRAb[53]

- Measurement of serum TRAb is important in pregnant patients undergoing evaluation for thyrotoxicosis for both diagnostic and prognostic reasons.
- Current guidelines recommend measuring TRAb at 20-24 weeks of gestation in patients with a past or present history of GD.
- Serum TRAb titers can also be used to help differentiate between postpartum thyrotoxicosis secondary to destructive thyroiditis and GD.

Imaging studies[53]

- Ultrasound: Thyroid ultrasonography, which measures thyroid volume and blood flow and can help distinguish GD from thyroiditis is a useful diagnostic tool in thyrotoxic pregnant women.
- Thyroid nuclear tests are not recommended during pregnancy.

Diagnosing thyrotoxicosis in pregnancy is challenging due to the overlapping clinical and biochemical characteristics of a typical pregnancy.[51] In pregnancy total T4 is preferred over fT4. fT4 measurements using the commonly available direct immunoassay lack standardization and show significant variability during pregnancy. Differences in results between assays and gestational age groups make it challenging to establish reliable reference ranges. More accurate techniques are available but are not widely accessible and are costly, limiting the use of FT4 measurements in pregnancy.[53] If facilities for total T4 are not available, then fT3 and fT4 are performed. A diagnosis of thyrotoxicosis is considered when we have elevated T3 and T4 levels above the pregnancy range and suppressed or undetectable TSH levels. In such situations, the presence of diffuse goiter, eye signs, and a high TRAb titer confirms GD (Figure 1).[54] TRAb cross placenta and can cause fetal thyrotoxicosis hence need to be investigated.[55]

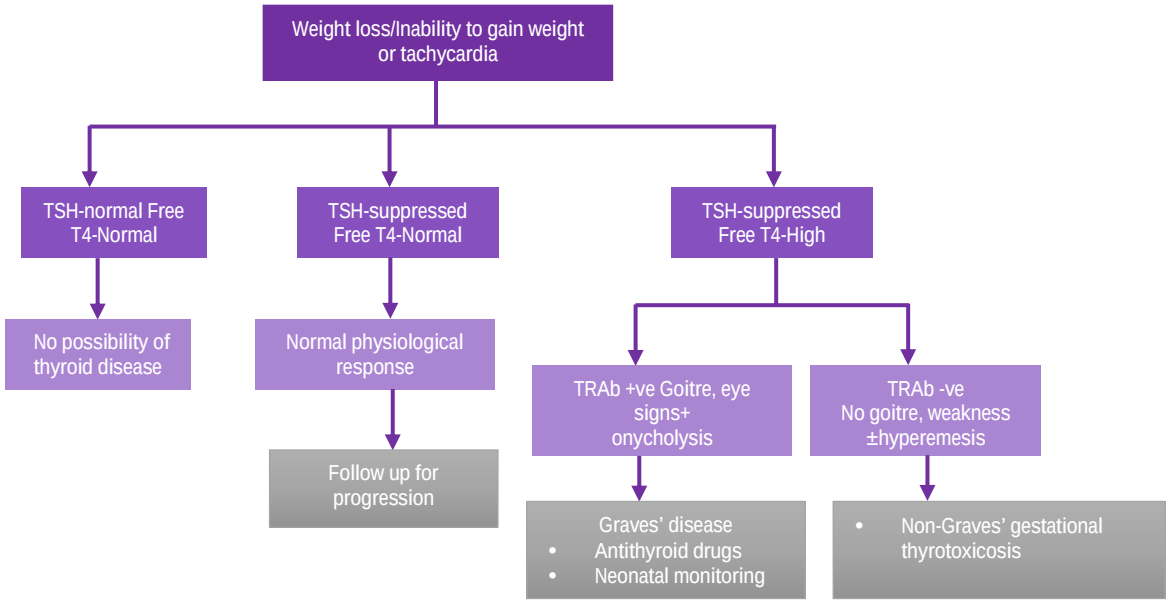

Figure 1: Workup of a patient with suspected hyperthyroidism during pregnancy.[54]

TSH: Thyroid stimulating hormone; T4: Thyroxine; TRAb: Thyroid stimulating hormone receptor antibody

- Clinical, laboratory and imaging tests will help differentiate between different causes of thyrotoxicosis in pregnancy (Table 9).[53]

Importance of differentiating between GD and GTT[56]

- Differential diagnosis between GD and GTT during early pregnancy is very important.
- Both conditions are associated with common clinical manifestations, but GTT does not require treatment with ATD and has not been associated with adverse pregnancy outcomes; hence, a careful history and physical examination are of utmost importance in establishing the etiology.

- GTT is diagnosed for the first time in early pregnancy and resolves by the end of the 1st or 2nd trimester of pregnancy.
- TSH is generally suppressed, T4 is elevated, and TRAb is absent. Other distinguishing characteristics between GTT and GD are elaborated in Table 12 below.

Table 12: Diagnostic clues regarding the etiology of thyrotoxicosis in the peri-pregnancy setting[51]

	GTT	Graves' disease	Toxic nodular goiter	Postpartum thyroiditis
The severity of thyrotoxic symptoms	Mild	Variable, may be severe	variable	Mild
Stigmata of Graves' disease	None	May be present: ▪ Diffuse goiter ▪ Thyroid bruit Ophthalmopathy	None	None
Presence of /emesis nausea	Yes, maybe severe	No	No	No
The ratio of serum T3:T4	<20:1	>20:1	>20:1	<20:1
Presence of TRAb	No	Yes	No	No

Treatment of GTT

- Supportive therapy with antiemetics, management of dehydration, electrolyte replacement, is often all that is needed.[51]
- Small doses of β-blockers given over a brief period may be helpful in certain circumstances.[52]
- Anti-thyroid drugs are not recommended.[52]

Recommendation

- A medical history, physical exam, and testing of the maternal blood free T4 or totalT4 concentrations should be performed when a suppressed serum TSH is found in the first trimester (a serum TSH below 0.1 mU/L (in some cases even undetectable) by week 11 (A/I)
- Serum total T4 and T3 levels more than 1.5 times the non-pregnant range should be used to diagnose thyrotoxicosis in 2nd and 3rd trimester of pregnancy.
- Measuring TRAb may be useful in determining the cause of thyrotoxicosis. (C/I)
- Radionuclide scintigraphy or radioiodine uptake determination should not be performed in pregnancy. (C/I)
- A careful history and physical examination is essential in establishing the etiology of GH and GTT for appropriate diagnosis. GH can be distinguished from GTT based on the presence of hyperthyroid symptoms prior to pregnancy, goiter, TRAb, and presence or absence of nausea/vomiting. (C/I)
- Anti-thyroid drugs are not recommended for the treatment of GTT. (C/I)

GD during pregnancy

Diagnosis

- GD is diagnosed with suppressed TSH, elevated FT4, and positive TRAb.[56]
- Maternal serum TSH and TT4/FT4 are the initial tests required for evaluation for hyperthyroidism in pregnancy.[56]
- Free T4 and TSH should be measured approximately every 2–4 weeks following initiation of therapy, and every 4–6 weeks after achieving the target value.[52]
- When trimester specific FT4 values are not available, the use of the reference range for nonpregnant patients is recommended. A TT4 measurement with a reference value 1.5 times the nonpregnancy range may be used in the second and third trimesters.[52]
- TRAb is ordered if tests are consistent with hyperthyroidism.[56]

Measurement of TRAb in women with GD during pregnancy

Serum TRAb levels should be determined in early pregnancy so that it can help in evaluating pregnancies at risk, and is helpful in a mother who is still in need of ATD therapy to remain euthyroid.

Treatment

- The treatment of GD in pregnancy is aimed to achieve maintaining total T3 and total T4 levels in the upper quartile of pregnancy-specific rangers with strict monitoring of maternal thyroid function at appropriate intervals. GD is treated by reducing TH synthesis, using ATD, or by reducing the amount of thyroid tissue by doing a thyroidectomy.[52,57.]
- Thyroidectomy is rarely required but may be performed in the second trimester.
- Free T4 and TSH should be measured approximately every 2–4 weeks following initiation of therapy, and every 4–6 weeks after achieving the target value.[52]
- Repeat TRAb testing should occur at weeks 18–22 if maternal TRAb concentration is elevated in early pregnancy, whereas no further TRAb testing is needed if it is undetectable or low in early pregnancy. A repeat determination of TRAb is recommended at weeks 18–22 if the patient requires treatment with ATDs for GD through mid-pregnancy. A TRAb measurement should again be performed in late pregnancy (weeks 30–34) to evaluate the need for neonatal and postnatal monitoring, if TRAb is elevated at weeks 18–22 or if the mother is taking ATD in the third trimester.[52]

ATDs for patients with GD

The initial dose of ATD depends on the severity of the symptoms and the degree of hyperthyroxinemia.[56] The starting dose of ATD should be gradually titrated according to the status of thyrotoxicosis. These should be measured approximately every 2–4 weeks following initiation of therapy, and every 4–6 weeks after achieving the target value.[52]

- PTU is the drug of choice in the first trimester with the starting daily doses of 100–200 mg.[3]
- In the second and third trimester, it is replaced with thionamides in doses of 10-20 mg.[3]

Prepregnancy euthyroid state must be attained in a patient of GD preferably by ablative therapy (RAI or surgery). In the case of RAI, conception should be deferred for atleast 6 months. Prepregnancy counselling should be initiated in all patients especially those who have a history of GD.[52]

Recommendation

- ✓ PTU is the drug of choice in the first trimester with the starting daily doses of 100–200 mg.(A/I)
- ✓ Free T4 and TSH should be measured approximately every 2–4 weeks following initiation of therapy, and every 4–6 weeks after achieving the target value (A/I)
- ✓ Thyroidectomy in pregnancy should be indicated in special situations with second trimester being the optimal time to conduct it. (C/I)
- ✓ Repeat TRAb testing at weeks 18–22 if initial levels were high or if ATDs are needed. No further testing if TRAb is low/undetectable. Test again at weeks 30–34 if TRAb was high at 18–22 weeks or if mother is on ATD in the third trimester for neonatal/postnatal monitoring assessment. (C/I)

Thyroid storm

Thyroid storm, also known as thyrotoxic crisis, is a severe, potentially fatal consequence of hyperthyroidism that manifests as multi-system involvement. It is a rare form of hyperthyroidism. Thyroid storm accounts for roughly 1% to 2% of hyperthyroidism admissions. Despite recent advances in treatment and supportive measures, the mortality rate associated with thyroid storm is estimated to be 8 to 25%. As a result, it is important to diagnose it early and begin aggressive therapy to prevent mortality.[58] Studies show that TS is a rare presentation of hyperthyroidism and accounts for about 1% to 2% of admissions for hyperthyroidism. The most common cause of death is multiple organ failure followed by congestive heart failure, respiratory failure, and arrhythmia.[59]

Precipitating factors[60]

- Inadequately controlled hyperthyroidism
- Abrupt cessation or non-adherence to Anti-Thyroid Drugs (ATDs)
- Administration of iodine-containing agents (e.g., amiodarone) or contrast agents (for CT imaging)
- Induction of anesthesia
- Neck stimulation in Graves' Disease (GD) with large goiter

Clinical presentation

- The clinical features of TS depend on the severity and duration of the condition, age, presence of extra-thyroidal manifestations, and the specific cause of the thyrotoxicosis.[60]
- In the elderly, the symptoms may be less marked than in younger patients.[60]
- Earliest signs include fever, tachycardia, diaphoresis, increased central nervous system (CNS) activity, and emotional lability. If left untreated a hyperkinetic toxic state occurs due to which symptoms are intensified. Progression to congestive heart failure, refractory pulmonary edema, circulatory collapse, coma, and death may occur within 72 hours. [60-61]
- CNS dysfunction may stimulate encephalopathy as the storm develops and intensifies, which may progress to include increasing agitation, emotional lability, confusion, paranoia, psychosis, and ultimately coma.[61]

- Gastrointestinal manifestations commonly present as diarrhea and vomiting, which can aggravate volume depletion, postural hypotension, and shock with vascular collapse. Rarely patients may present with liver dysfunction, jaundice, and hepatic failure.[61]

Diagnosis

Diagnosis of TS involves using a combination of biochemical laboratory tests confirming thyrotoxicosis in a patient displaying the severe, life-threatening symptoms of hyperthyroidism.[62]

Treatment

- A multimodal treatment approach is followed in which multiple medications that targets various causes and effects of thyrotoxicosis are included.[62]
- Fluid replacement is necessary as thyrotoxic patients are fluid-depleted due to fever, diaphoresis, as well as by vomiting, and or diarrhea and any delay may lead to vascular collapse. Judicious replacement of fluids is crucial for elderly patients with tachyarrhythmias or congestive heart failure.[61]
- IV fluids, oxygen, cooling, and treatment of any precipitating factors are examples of supportive measures.[61-62]
- β-blocker therapy is effective in symptomatic improvement of tachycardia and clinical manifestations reflecting the increased adrenergic tone.[62] Typically, propranolol 40 mg to 80 mg is given every 4 to 6 hours.[58]
- ATD should be initiated to reduce TH production.[59] Either a loading dose of propylthiouracil (PTU) 500 mg to 1000 mg followed by 250 mg every 4 hours or Methimazole (MMI) 20 mg every 4 to 6 hours should be given. Propylthiouracil is preferred because it has a small additional effect of blocking the peripheral conversion of T4 to T3.[58]
- Glucocorticoids (Dexamethazone IV 2 mg every 6 hours) also reduces the peripheral conversion of T4 to T3.[61]
- Saturated solution of potassium iodide should be administered to inhibit the release of TH from the thyroid gland.[62]
- Bile acid sequestrants such as cholestyramine is effective to reduce TH levels in thyrotoxic patients by interfering with enterohepatic circulation and recycling of TH. It can be used as an adjuvant therapy in patients who cannot tolerate ATD.[61]
- Lithium can also be rarely used in case of contraindication or toxicity to ATD.[61]
- Plasmapheresis may rarely be required.[62]

Recommendation

- A multimodality treatment approach to GD patients with thyroid storm is recommended, including ATD therapy, glucocorticoid administration, β-adrenergic blockade, volume resuscitation, nutritional support, respiratory care, and monitoring in an intensive care unit. A/ IIb

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