SAFES Clinical Practice Recommendations for Management of Hypothyroidism and Hyperthyroidism
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Hypothyroidism

Introduction

Hypothyroidism is characterized by the thyroid gland's inability to generate enough thyroid hormone to fulfill the body's metabolic demands. Hypothyroidism, if left untreated, can lead to hypertension, dyslipidemia, infertility, cognitive impairment, and neuromuscular dysfunction.[1] Hypothyroidism can present with a wide spectrum of clinical manifestations, from potentially fatal symptoms to no symptoms at all. The clinical presentation might vary with age and sex, among other factors; nonetheless, fatigue, lethargy, cold intolerance, weight gain, constipation, voice change, and dry skin are the most common symptoms in adults.[2] Since most hypothyroidism symptoms are nonspecific, laboratory tests are necessary for diagnosis. A high thyroid stimulating hormone (TSH) level nearly typically indicates primary hypothyroidism. Oral L-thyroxine is the preferred treatment due to its efficacy, safety, and ease of use. The goals of therapy are to relieve symptoms and keep serum TSH levels in the reference range.[3]

Definition

Overt or clinical primary hypothyroidism is defined by TSH levels above the reference range and free thyroxine (T4) levels 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 free T4 levels within the normal range.[3] In healthy individuals, the reference range is typically statistically defined by the 2.5th and 97.5th percentiles of the measured circulating thyroid hormone concentrations.[4]

Epidemiology

It is estimated that 1.3% of the population has hypothyroidism, with the incidence rate being 2.7% in females and 0.7% in men.5 In India, the prevalence of hypothyroidism is 11%, compared to 2% in the UK and 4.6% in the US.6 Table 1 summarizes the prevalence of hypothyroidism and subclinical hypothyroidism in major South Asian countries.

Table 1: Prevalence of hypothyroidism in South Asian countries

Country	Hypothyroidism	Subclinical hypothyroidism
India[7]	10.95%	8.02%
Sri Lanka[8]	6.1%	9.4%
Bangladesh[9]	3.80%	3.46%
Pakistan[10]	4.1%	5.4%
Afghanistan[11]	12%	_

Etiology

Hypothyroidism can be divided into four types: primary (caused by a lack of thyroid hormone), secondary (caused by a lack of TSH), tertiary (caused by a lack of thyrotropin-releasing hormone), and peripheral (extra-thyroidal). Central (including secondary and tertiary) and peripheral hypothyroidism are uncommon, accounting for less than 1% of cases.[2]

Primary hypothyroidism

Autoimmune (Hashimoto's) thyroiditis is the leading cause of hypothyroidism in the majority of persons, particularly women, in iodine-sufficient regions of the world.[2] Other causes include radioiodine therapy for hyperthyroidism, surgical thyroid removal, and a variety of medicines that either inhibit thyroid function or cause thyroid inflammation; congenital lack of the thyroid, or inborn defects of thyroid hormone production

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(dyshormonogenesis) (Table 2). While the majority of forms of autoimmune thyroiditis result in hypothyroidism, this condition is typically temporary rather than permanent in patients with mild TSH elevation.[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—e.g., 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 produces T4 (thyroxine) and T3 (triiodothyronine) hormones through the use of iodide obtained from food or metabolism. It takes around 100 µg of iodide per day to produce sufficient thyroid hormone. The thyroid's epithelial cells have a Na/I symporter that concentrates iodide 30 to 40 times higher than in plasma to make sure there's enough for hormone production. The iodide is then oxidized to iodine by thyroid peroxidase and undergoes organic reactions in the thyroid to produce T4 and T3. T3 can also be produced in other organs like the pituitary, liver, and kidney by removing an iodine from T4. T4 is considered a pro-hormone and T3 is the most potent hormone produced. T4 and T3 are stored in the thyroid's thyroglobulin protein and are released into circulation by TSH (thyroid stimulating hormone). A normal person produces around 90-100 µg of T4 and 30-35 µg of T3 daily. Most of the T3 produced in humans (80%) is obtained from peripheral metabolism of T4, and only 20% comes directly from the thyroid. T3 is 3-5 times more potent than T4 as a thyroid hormone and is believed to be the active form. T4 binds mostly to TBG (~75%) and weakly to TBPA and albumin. T3 binds tightly to TBG and weakly to albumin. Normal T4 levels are around 8 µg/dl and T3 levels are around 130 ng/dl. Almost all T4 and T3 in serum are protein-bound, with only a small amount of free T4 (2 ng/dl) and T3 (0.3 ng/dl) that are responsible for biological effects.

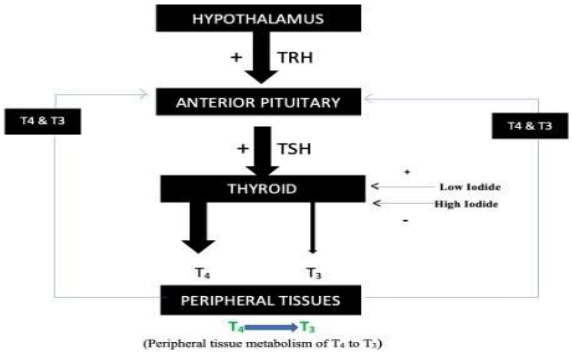

Figure 1: Pathway for secretion of thyroid hormones13 (The hypothalamic-pituitary-thyroid axis governs thyroid hormone secretion. Levels of circulating thyroid hormones are regulated by a complex feedback system involving the hypothalamus and pituitary gland.)

Certain binding proteins in serum bind T4 specifically. These include T4-binding globulin (TBG), transthyretin, T4-binding prealbumin, and albumin to a lesser extent. Since 99.97% of T4 is bound to proteins, factors that alter binding will have an effect on serum total T4 levels regardless of thyroid disease (Table 3).14 As with T4, T3 is likewise bound to serum proteins, mainly TBG, although to a lesser level (99.7%). However, in hypothyroidism, measuring serum T3 (total or free) is of little use because levels are typically normal due to hyperstimulation of the remaining functional thyroid tissue by increased TSH and to up-regulation of type 2 iodothyronine deiodinase.15 As a result, basing clinical judgments on a free T4 in the context of a normal TSH is associated with complications in most cases.[15]

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Table 3: Factors That Alter Thyroxine and Triiodothyronine 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		

Clinical features

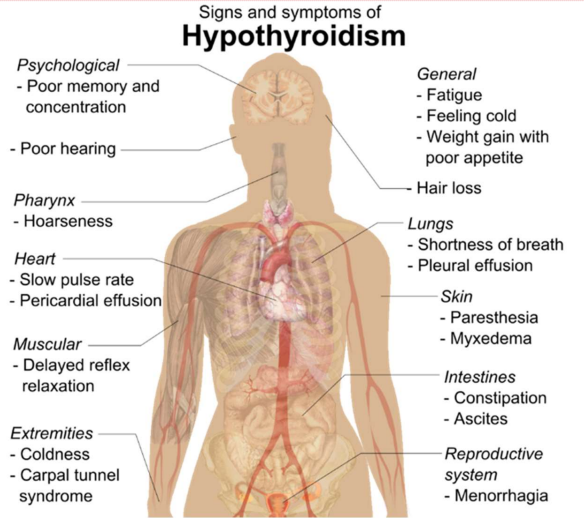
Common symptoms

The symptoms of hypothyroidism are less obvious than those of hyperthyroidism. Constipation, dry skin, cold sensitivity, fatigue, muscle cramps, and voice changes are common symptoms of hypothyroidism (Figure 1).[14]

Less common symptoms of hypothyroidism

Less prevalent and related to severe hypothyroidism are carpal tunnel syndrome, sleep apnea, pituitary hyperplasia with or without hyperprolactinemia and galactorrhea, and hyponatremia that can emerge within weeks after the onset of profound hypothyroidism.[14]

Figure 2: Common symptoms and signs associated with hypothyroidism4



Clinical manifestations

Hypothyroidism has clinical implications related to nearly all major organs, but the cardiovascular system is the most robustly studied. Other manifestations include neurosensory, musculoskeletal, and gastrointestinal signs and symptoms.[2] (Table 4).

Table 4: Clinical presentation and implications of hypothyroidism		
	Presentation	Signs and implications
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)
Hemostasis and 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 kidney function	Deterioration of kidney function	Decreased estimated glomerular filtration rate, hyponatremia*
*Uncommon presentation		

Recommendation

- Symptoms alone lack sensitivity and specificity and are not recommended for evaluating replacement adequacy in the absence of biochemical evaluation. Symptoms should be monitored, but in the context of serum TSH levels, associated comorbidities, as well as other probable causes. (A/I)

Diagnosis

TSH is the primary test for diagnosing thyroid dysfunction and evaluating thyroid hormone replacement in primary hypothyroidism.14 TSH at the low end of normal is 0.4 mIU per L. The upper end of the normal range is 4.0 to 4.5

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mIU per L. The level of free thyroxine (FT4) is used to differentiate clinical (low FT4) from subclinical (normal FT4) hypothyroidism. It is not recommended to routinely evaluate total T3, total T4, or FT3 levels. Thyroid peroxidase antibody (TPOAb) testing does not aid in the diagnosis of hypothyroidism; nevertheless, a positive test result suggests an autoimmune cause. Thyroid ultrasonography is used to assess palpable thyroid nodules and is not routinely performed.16 Table 5 provides a 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

Hypothyroidism patients may have abnormal complete blood values and metabolic profiles.18 General laboratory abnormalities provide suggestive but not definite clues to the diagnosis of hypothyroidism; frequent results include hyponatremia, macrocytic anemia, and increased creatine kinase levels. Hypothyroidism also produces mixed hyperlipidemia, which is characterized by an increase in all lipids and lipoproteins [total, low-density lipoprotein, and high-density lipoprotein cholesterol; triglycerides; and lipoprotein(a)].[3]

Recommendation

- TSH is the primary test used to diagnose thyroid dysfunction, evaluate thyroid hormone replacement in primary hypothyroidism, and evaluate suppressive medication in follicle cell-derived thyroid cancer. (A/I)
- Neither serum total T3 nor serum free T3 should be assessed to diagnose hypothyroidism. (C/IIa)
- The measurement of anti–thyroid peroxidase antibody (TPOAb) should be considered when evaluating patients with subclinical hypothyroidism. (A/I)

Treatment

Levothyroxine (LT4) therapy is the cornerstone of hypothyroidism treatment. LT4 is the preferred preparation for the treatment of hypothyroidism because of its effectiveness in alleviating symptoms, long-term experience with its advantages, benign side effect profile, the convenience of administration, excellent intestinal absorption, extended serum half-life, and low cost.[14]

- The primary aims of LT4 replacement treatment are as follows:[14]
  - To provide symptomatic relief
  - To normalize thyroid function tests
  - To maintain patients in a euthyroid state
- The patient's weight, lean body mass, pregnancy, cause of hypothyroidism, degree of TSH elevation, age, weight, and presence of comorbid conditions, especially heart disease should be considered when determining a starting dose of LT4.[19]
- Hypothyroid patients with low endogenous thyroid activity require LT4 dosages of 1.6-1.8 µg/kg of body weight.[19]
- Experts advise that, if feasible, LT4 be routinely administered either 60 minutes before breakfast or at bedtime (3 or more hours after the evening meal) for optimal, consistent absorption because co-administration of food and LT4 is likely to decrease LT4 absorption.[19]
- Serum TSH levels should be measured in patients with established hypothyroidism 4-8 weeks after initiating treatment or after a dose modification. Once an appropriate replacement dose has been identified, periodic TSH measures should be

performed after 6 months and subsequently at 12-month intervals, or more frequently if the clinical situation demands it.[14]
- Although daily administration of LT4 is ideal, missed doses must be administered as soon as they are recognized, even on the same or subsequent days.[19]
- Patients receiving LT4 replacement for hypothyroidism should have blood drawn before dosing so that serum-free T4 levels may be assessed.[15]

Indications of prescribing LT3

Liothyronine (LT3) is generally indicated in patients of hypothyroidism who are biochemically euthyroid but continue to have symptoms of hypothyroidism. Currently, LT3 monotherapy is only used in the treatment of severe hypothyroidism with myxedema coma. Short-term LT3 medication is also beneficial in patients with differentiated thyroid cancer who are being tapered off LT4 before 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.
- The foundation for these suggestions is that cost-effective diagnostic assessments and improved results in the medical and surgical evaluation and management of thyroid disorders such as nodular thyroid disease and thyroid cancer are favorably linked to the volume of a surgeon's experience or if the patient was reviewed by an endocrinologist.
- Finally, compared to obstetricians, gynecologists, internists, and family doctors, endocrinologists have more familiarity with the link between thyroid disease and pregnancy.

Recommendation
- LT4 therapy is the cornerstone of hypothyroidism treatment. (A/I)
- Hypothyroid patients with low endogenous thyroid activity require LT4 dosages of 1.6-1.8 µg/kg of body weight. (A/I)
- Serum TSH levels should be measured in patients with established hypothyroidism 4-8 weeks after initiating treatment or after a dose modification. Once an appropriate replacement dose has been identified, periodic TSH measures should be performed after 6 months and subsequently at 12-month intervals, or more frequently if the clinical situation demands it. (A/I)

Screening and aggressive case finding for hypothyroidism

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

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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

Recommendation

- Screening is recommended for all those individuals who have a strong index of suspicion (A/I)
- In high-risk patients, such as elderly women (<60 years), screening may be beneficial (A/I)
- Given the non-specific symptoms of hypothyroidism, widespread screening is unlikely to be cost-effective (A/I)

Refractory Hypothyroidism

Refractory primary hypothyroidism is defined as biochemical or clinical evidence of hypothyroidism [serum level of TSH beyond the upper goal level, generally 4.5 mU/L following a 6-week interval after the dosage was last increased] and/or unresolved hypothyroid symptoms despite increasing dosages of LT4 above 1.9 µg/kg daily. Further increases in LT4 dosage may not always be the best course of action, as iatrogenic hyper has been linked to adverse cardiovascular outcomes and bone health. Clinicians should verify compliance and look for reasons for poor absorption or a higher need for LT4 when dealing with instances where unexpectedly large dosages of LT4 are needed (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]

Recommendation

- Thyroid hormone resistance to oral thyroxine replacement when there is biochemical or clinical evidence of hypothyroidism (serum TSH beyond the upper target level, generally 4.5 mU/L after the dosage was last raised) despite increasing oral thyroxine dosages above 2.5 µg/kg daily. (C/IIa)
- Increasing the dosage of LT4 in a patient

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until the desired TSH levels are reached is a standard method for the management of patients who have atypical thyroxine requirements. Clinicians should adopt a systematic approach to treating individuals who have treatment-resistant hypothyroidism. (C/IIa)

Myxedema Coma

- Myxedema coma is a life-threatening endocrine emergency. In addition to age, concomitant cardiovascular disease and treatment with high-dose LT4 replacement therapy may be related to an increased risk of mortality.[23]
- Myxedema coma is a serious, life-threatening condition that arises more likely due to sepsis, cerebrovascular accidents, congestive heart failure, or incorrect pharmacological therapy, such as excessive diuretic use for hypertension and edema resulting in hyponatremia, sedatives, and antidepressants.[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, congestive heart failure, ileus, hypoventilation with hypercapnia and respiratory acidosis are possible complications.[23]
- Pericardial effusions may be frequently associated.[23]
- Severe hypothyroidism may be accompanied by hyponatremia, hypoglycemia, and/or adrenal insufficiency.[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 µg of intravenous LT4 may be followed by 50 µg daily.[23]
- Depending on the risk of cardiovascular disease, a loading dosage of 5-25 µg of LT3 may be delivered concomitantly followed by 2.5-5 µg 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 often available in India, most hospitals substitute parenteral therapy with crushed LT4 tablets administered through a nasogastric tube. The initial dose is often between 300-500 µg, followed by 100 µg per day. This route is unfavorable because it not only raises the risk of irregular absorption, especially in patients with stomach atony but also the risk of 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 (NHANES III) study revealed that the highest limit of the reference range (confidence interval of

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97.5%) rises from 3.56 mU/l in 20-29-year-olds to 7.9 mU/l in those older than 80 years.[23]

- Consequently, it will be crucial to evaluate these age-related variations in TSH levels when diagnosing hypothyroidism.[23]

Symptoms and signs [23-24]

- Although elderly people with hypothyroidism may appear with characteristic symptoms, their complaints are often less specific than those described by younger patients with thyroid hormone shortage.
- This may be related, in part, to patients and physicians attributing nonspecific symptoms to various comorbid diseases that are frequent among the elderly or to the consequences of aging itself.
- Complaints of cold intolerance, weight gain, paresthesias, and muscle cramps were less common among the elderly.
- Hypogeusia and dysgeusia, hearing loss, and ataxia are other neurological symptoms that have been observed to be more prevalent in elderly people.
- In the elderly the clinical manifestations of hypothyroidism include bradycardia, diastolic hypertension, pallor, dry skin, coarse hair, hoarseness, dysarthria, delayed deep tendon reflexes, and mental state abnormalities.
- Comorbid cardiovascular, neuropsychiatric, dermatologic, or rheumatologic disorders that are more common in the elderly may worsen the severity of specific findings.

Treatment of hypothyroidism in the elderly

- While LT4 is recommended as the first-line treatment for hypothyroidism in the elderly, it should be used with caution.[25]
- Initiating LT4 therapy at low dosages and gradually increasing the dose in response to serum TSH levels is recommended. Normal serum TSH ranges are higher in elderly populations (such as those over 65 years old), so setting higher serum TSH targets may be warranted.[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 µg daily, regardless of the severity of their hypothyroidism. In patients with established CHD, the initial dose is typically lowered to 12.5-25 µg/day.[14]
- It is recommended to gradually increase the dosage by 25 µg 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 may have negative effects on maternal and fetal outcomes, especially in TPOAb-positive women.14 Table 8 gives you a list of 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]

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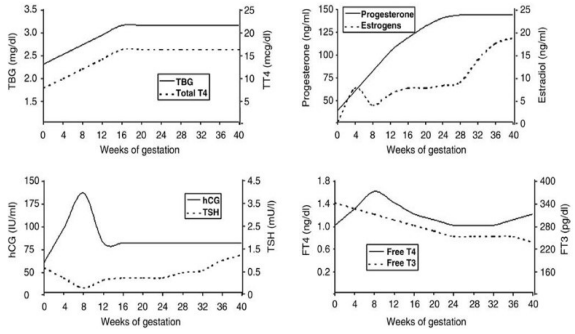
- This risk may be a result of diminished thyroid functional reserve brought on by persistent autoimmune thyroiditis, which can lead to mild hypothyroidism.[14]

Diagnosis of maternal hypothyroidism

- Thyroid function assessment during pregnancy is challenging, as the physiologic changes (increase in TBG, placental deiodinase activity, urinary iodine excretion, and increase in hCG secretion), cause a downward shift of TSH reference intervals, and makes it difficult to interpret maternal thyroid function tests. Hence, if nonpregnant TSH reference intervals are applied to pregnant women, it would lead to underdiagnosis of hypothyroidism or overdiagnosis of hyperthyroidism.[27]
- The ATA 2017 guideline suggests that the TSH reference range should be pregnancy and trimester-specific and developed from a local population that is iodine-sufficient, TPO antibody-negative, and free from any underlying thyroid disorder. In case of unavailability of locally derived reference ranges. When local assessments are not available, the lower reference range of TSH can be reduced in 1st trimester of pregnancy by approximately 0.4 mU/ (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 TBG rise. In healthy pregnant women, thyroid function test findings differ from those of healthy non-pregnant women. This necessitates pregnancy-specific and preferably trimester-specific reference ranges for all thyroid function tests, but especially for the most often used assays, TSH, free T4, total T4, and total T3.[29]

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



Abbreviation – TBG: Thyroxine binding globulin; hCG: Human chorionic gonadotrophin; TSH: Thyroid stimulating hormone

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 µg/kg/d) and should be counseled on the importance of treatment adherence and the necessity

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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

- It is important to examine the etiology and trimester-specific changes in thyroid physiology while treating 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

- Many prospective and retrospective investigations have found that modestly higher maternal TSH concentrations are related to an increased risk of pregnancy problems, particularly in TPOAb-positive women. But only a few studies have examined how LT4 treatment affects pregnancy complications in these women. A single RCT showed a possible advantage of LT4 intervention at *9 weeks gestation.28
- Importantly, the study found a reduction in unfavorable pregnancy outcomes only among TPOAb-positive women with mild hypothyroidism (defined as a TSH >2.5 mU/L).[28]
- Thyroid peroxidase antibodies (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]
- Despite the few interventional trials of LT4 medication in this subclinically hypothyroid group, the evidence suggests a benefit, especially in lowering miscarriage in TPOAb-positive women.[28]
- Therefore, LT4 therapy seems reasonable for certain pregnant women with subclinical hypothyroidism. The degree of such recommendations and the evidence supporting treatment for each subgroup

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should vary by TPOAb status. [28]

- Pregnant women with a high TSH must also be tested for TPOAb. In making its decision, the task committee recognizes the very low risk of starting low-dose LT4 treatment.[28]
- Typically, only 50 µg/d is needed to effectively treat subclinical hypothyroidism in women.[28]

Recommendations

Treatment of women with isolated hypothyroxinemia in pregnancy[28]

- Several studies have indicated unfavorable outcomes in children born to mothers with isolated hypothyroxinemia, but no interventional data have shown the benefits of LT4 therapy.
- A 12-week, 24-week, and 32-week observational research found impaired infant neurodevelopment in women with persistent hypothyroxinemia. However, infant growth was not enhanced when FT4 concentrations increased during pregnancy. Currently, there are just two randomized, prospective trials in which women with low FT4 were treated with LT4 at 13- and 17 weeks gestation.
- Both studies found no benefit in cognitive development after LT4 administration, even though the intervention was given after the first trimester had ended.
- Nonetheless, given the available interventional data, therapy of isolated hypothyroxinemia is not currently recommended.

Role of iodine[28]

- Due to increased thyroid hormone synthesis, renal iodine excretion, and fetal iodine needs, dietary iodine needs are higher in pregnancy.
- Adequate iodine intake before and during pregnancy helps women adjust to the increased demand for thyroid hormones during pregnancy. Breast milk secretes iodine for baby nourishment. As a result, lactating women have increased dietary iodine requirements.
- Maternal dietary iodine deficit impairs thyroid hormone synthesis. Low thyroid hormone levels enhance pituitary TSH production, which causes maternal and fetal goiter.
- In areas with severe iodine deficiency, up to 30% of pregnant women may have thyroid nodules. Severe iodine shortage in pregnant women increases pregnancy loss, stillbirth, and perinatal, and infant mortality.
- Normal thyroid hormone levels are needed for neuronal migration, myelination, and other embryonic brain processes.
- Iodine deficiency affects both maternal and fetal thyroid hormone production during pregnancy, and inadequate iodine consumption might have negative consequences. Iodine shortage during pregnancy affects offspring's cognitive performance.
- Children of iodine-deficient mothers may have cretinism, which causes intellectual disability, deaf-mutism, and motor stiffness. Iodine shortage causes intellectual deficiencies worldwide.
- Iodine is needed for thyroid hormone production and is mostly obtained from diet and vitamin/mineral supplements. The U.S. Institute of Medicine recommends 150 µg/d for women contemplating pregnancy, 220 µg/d for pregnant women, and 290 µg/d for lactating women as total daily iodine intake targets. The World Health Organization recommends 250 µg/day for

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pregnant and lactating women.

Subclinical hypothyroidism

Introduction

Subclinical hypothyroidism (SCH) is defined as a state of increased serum thyroid-stimulating hormone (TSH) levels, with circulating T4 and T3 concentrations within the population reference range. SCH should be considered in two categories according to the elevation in serum thyroid stimulating hormone (TSH) level:[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). Both exogenous, and endogenous factors cause SCH. The endogenous factors include sub-acute thyroiditis, and chronic autoimmune thyroiditis, whereas, the exogenous 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

Most frequently, SCH is asymptomatic. However, it can manifest hypothyroidism symptoms. 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

Recomendations

- 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

Asymptomatic patients with blood TSH between 4.5 and 10 µU per mL should have a repeat test every six to 12 months. Available evidence does not demonstrate a benefit for early treatment of subclinical hypothyroidism; hence, the panel does not suggest treatment with LT4 for these patients. In hypothyroidism individuals with serum TSH between 4.5 and 10 µU per mL, there is inadequate evidence to warrant therapeutic action.[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

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disease. Lipid profiles should be checked. Women who are pregnant or intend to become pregnant in the near future deserve special consideration.[38]

The data was insufficient to warrant routine TPOAb testing in subclinical hypothyroidism. TPOAb positivity indicates an autoimmune etiology for thyroid dysfunction and predicts a higher likelihood of developing overt hypothyroidism (4.3% vs 2.6% in antibody-negative persons). Antibody presence or absence does not affect subclinical hypothyroidism diagnosis (based on serum TSH levels) or therapy efficacy.38 Factors favoring the treatment of SCH are listed in Table 11.[39]

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 patients with SCH between 2.5 and 4.5 mIU/L

- No clinical data have supported treating patients with SCH having TSH levels between 2.5 and 4.5 mIU/L. Exceptions may be pregnancy due to increased risk of complications in anti-thyroid antibody-negative women with TSH values between 2.5 and 5.0 mIU/L such as pregnancy loss, spontaneous miscarriage before 20 weeks gestation, and stillbirth after 20 weeks.[14]

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 OH, and mortality.
  - o Individuals with TSH 4.5-9.9 mU/L who are healthy and asymptomatic do not require treatment.
  - o 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.
  - o 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 of choice 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]
- Treatment for those with TSH less than 7

mIU/L may not be of any benefit. The authors conclude that LT4 doses should be personalized according to age, comorbidities, and life expectancy in elderly aged ≥65 years.41

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.

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]

Recommendations

- Patients (<65 years of age) with TSH 4.5-9.9 mU/L who are healthy and asymptomatic do not require treatment, but those with a higher risk of progression to overt hypothyroidism (female gender, a progressive increase of TSH levels, positive TPOAb) may be considered for treatment. (C/I)
- Treatment of elderly (≥65 years of age) should be based after weighing the risks and benefits as this category of patients are at a higher risk of overtreatment and are more susceptible to adverse consequences and depends on the decision by the treating Physician, and an Endocrinologist. (C/I)
- The dose of LT4 should be personalized according to age, comorbidities, and life expectancy in elderly aged ≥65 years. (C/I)
- In individuals with TSH >10 mIU/L; treatment can be considered in those <70 years, whereas, a watch and wait approach can be followed or treatment can be considered if clear symptoms or high cardiovascular risk is present in the older population ≥70 years. (C/IIa)
- In individuals with TSH <10 mIU/L; treatment should be considered for <70 years with symptoms, whereas those without symptoms can be under observation, whereas those >70 years can be under observation. (C/IIa)
- An approach of effective decision-making should be followed while treating SCH and all relevant clinical data such as the patient's age, TSH level, quality of life, comorbidities, cardiovascular risk, safety,

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should be considered for a thorough investigation. (C/I)
- Patients with SCH having TSH levels between 2.5 and 4.5 mIU/L do not require treatment. (C/IIa)

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 those who are asymptomatic, have negative thyroid autoantibodies, or do not have goiter. 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]

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

There is insufficient evidence of benefit to recommend that treatment with LT4 be targeted to achieve low-normal TSH or high-normal T3 levels in patients with hypothyroidism who have dyslipidemia or are athyreotic.14 Thyroid hormone replacement therapy is beneficial for severe and mild SCH patients with 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 that TSH has fallen into the reference range. Furthermore, if there was hypercholesterolemia or other dyslipidemia before starting LT4, it is worthwhile to re-check the serum lipid profile to see if there has been adequate improvement or if additional dyslipidemia therapy is required. At this point, it is also worthwhile to re-evaluate hypothyroidism symptoms in those SCH individuals who were started on therapy for hypothyroidism 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. These findings suggest that 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 moderate thyroid dysfunction are prevalent disorders that can coexist clinically. Clinicians should be more cautious about the possibility of thyroid disease in obese patients. The difficulty arises in recognizing obese individuals with modest thyroid hormone insufficiency. Treatment of overt hypothyroidism results in relatively modest

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weight reduction, but not necessarily in all individuals. Thyroid hormones have been used to cause weight loss in obese euthyroid patients, but only obese hypothyroid subjects should be given them to regulate body weight.[46]

Cardiovascular diseases

A cross-sectional adult population survey was carried out on a total of 986 community-dwelling volunteers in Southern India to investigate the effect of subclinical hypothyroidism on cardiovascular health. The ten-year risk of an adverse cardiac event was calculated using the Framingham score algorithm. This sample had significant baseline rates of diabetes (19.5%), hypercholesterolemia (57.2%), and systolic hypertension (24%). Subclinical hypothyroidism or increasing TSH did not affect Framingham's 10-year risk. While lipid profiles did not differ between groups, increased TSH was connected with modest lipid profile worsening.[47]

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

For those with known CVD, the American Thyroid Association guidelines for hypothyroidism treatment recommend starting LT4 at a low dose, gradually increasing as needed, and closely monitoring for the development of cardiac symptoms.5 Most international societal guidelines currently recommend that treatment decisions be individualized based on patient age, degree of serum TSH elevation, symptoms, CVD risk, and other co-morbidities. Treatment of SCH with LT4 must be initiated with caution in elderly patients. It should be noted that different reference intervals apply to specific subpopulations (the elderly, and pregnant women), which may influence the decision to treat or not treat with LT4.[48]

Depression

LT4 monotherapy in solid form, administered on an empty stomach, is the preferred treatment for hypothyroidism. Treatment should be started when hen 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 persons.19 In overt hypothyroidism, the optimum daily dosage is 1.5-1.8 µg per kg of body weight.19, 33, 49 For people with coronary artery disease, the starting dose is usually 12.5-25.0 µg per day, and it should be gradually increased based on symptoms and TSH levels. TSH levels are monitored after 4-12 weeks of medication, every six months, and, if the patient is stable, annually. Adjustments should be made based on laboratory findings because even modest dosage adjustments can have a considerable impact on serum TSH concentrations in some people (e.g., those with low body weight or those who are elderly). Despite having normal TSH levels, low T3 levels in certain individuals are of little therapeutic significance. Routine T3 levels should not be used to assess therapeutic success.[50]

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