بسم الله الرحمن الرحيم

ENDOCRINE DISEASE AND ELDERLY

- THYROID DISEASE
- DM

THYROID CHANGES WITH AGING INTRODUCTION

- Disorders of thyroid function increase with aging, affecting approximately 20% of those over 65 years old
- Factors that can make it difficult to diagnose thyroid dysfunction in the elderly

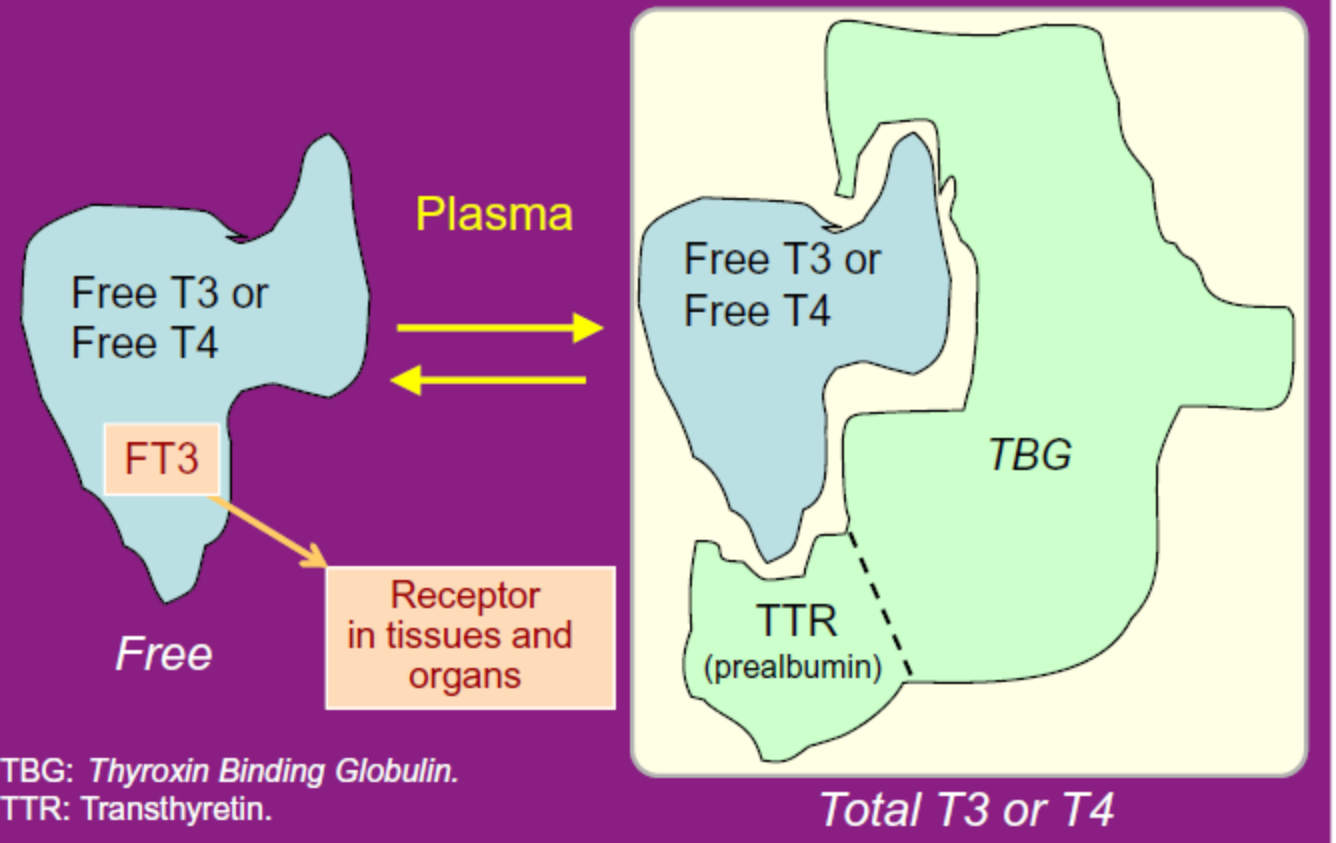
  population include:

  - Comorbidities and nonthyroidal illnesses
  - Concomitant use of certain drugs, in particular: amiodarone, iodine contrasts agents, tyrosine-kinase inhibitors, and immune checkpoint inhibitors
- Physiological changes in the hypothalamic-pituitary-thyroid axis

- Morphological thyroid changes in the elderly
  - Initial autopsy studies: Reduced thyroid weight with smaller thyroid follicles
  - The gland is positioned more caudally
  - Ultrasound studies: Thyroid volume does not change
  - Tendency for increased fibrosis and nodule formation
- THYROID FUNCTION MODIFICATIONS
  - Thyrotropin (TSH)
- Cross-sectional studies:
  - The average concentration and upper reference limit of serum TSH tend to shift to higher values with aging in healthy subjects without evidence of thyroid autoimmunity
- The proportion of people with altered serum TSH values is higher in older versus

- Free T4 does not change significantly in the elderly
- The metabolic clearance rate (MCR) of T4 decreases linearly with aging
- As a result, LT4 requirements decrease in the elderly hypothyroid patients

Transport of thyroid hormones



TBG: *Thyroxin Binding Globulin.*
TTR: Transthyretin.

The binding protein TBG, decreases with age but is compensated for by an increase in Transthyretin, so that the peripheral transport of hormones does not change.

Triiodothyronine (T3)

- T3 changes with age are controversial due partly to the influence of extrathyroidal diseases
- Extrathyroidal illnesses alter the transport of both T4 and T3 and the peripheral conversion of T4–T3

PRIMARY HYPOTHYROIDISM IN THE ELDERLY SPECIAL CLINICAL CHARACTERISTICS

- Clinical manifestations:
  - May be less evident because they are confused with signs and symptoms of other age-related syndromes
- Diagnosis:
  - Thyroid function tests can be altered by the presence of non thyroidal diseases and because circulating TSH concentrations increase with aging

❑ Treatment:

- Dosage differs from that in younger adults due to
  - the reduced metabolic clearance rate of thyroid hormone, pharmacological interactions, and potential adverse reactions (e.g. arrhythmias)
- Prevalence and incidence: Higher in older individuals

EPIDEMIOLOGY

- Prevalence in the elderly
  - Depends on the population studied and the criteria employed 7%–14% greater in women versus men
- Europe: More prevalent in elderly people from areas with high iodine intake

The prevalence of subclinical hypothyroidism is determined by the upper limit of normality defined for TSH. Because serum TSH concentrations increase with age2,13,14 the true prevalence in older age is likely not as high as described in many studies.

ETIOLOGY

- Hypothyroidism in persons >55 years :
  - 57% is due to chronic autoimmune thyroiditis,especially the atrophic form,
  - 32% is postsurgical
  - 12% postradioiodine
  - only 2% is of central origin

Autoimmune chronic thyroiditis

- 75% have positive antithyroid antibodies
- Positive antithyroid antibodies in general healthy population: Antithyroid peroxidase (TPO) 11.3%, antithyroglobulin (anti-TG) 10.4%
- Positive antithyroid antibodies are more common in women than in men and increase with age but are less prevalent in centenarians and very old people in good health
- Positive anti-TPO antibodies are associated with the development of hypothyroidism more often than positive anti-TG antibodies Positive anti-TPO levels increase the risk of developing hypothyroidism by 4.3% per year
- titer is not predictive

Postradioiodine ablation treatment

- Initially, 20%–40%. Then, 0.5%–2% per year. 10-year incidence: 40%–80%
- In persons >55 years: 12% during the 1st year; then 8% annually
- Less common in patients with hyper functioning multinodular or uninodular goiter
- Sometimes transient hypothyroidism in the first 3months
- Thyroid function should be monitored in all patients

Postsurgical

- Variable incidence (1st year 20%–40%, then 2%–4% annually) depending on the cause and type of surgery
- Transient elevation of TSH (for about 1 year)

Medications

- medications that induce thyroid dysfunction (e.g., amiodarone, tyrosine kinase inhibitors, or immune checkpoint inhibitors)

- EFFECTS OF DRUGS ON THE THYROID

- Thyroid hormone control, synthesis, release, transport, and metabolism may be interfered by a wide variety of medications, and many of these are used preferentially by elderly patients

Drug effect	Compound	Condition/test results
Disruption of hypothalamic-pituitary control	• Retinoid bexarotene • Mitotane • Immune checkpoint Inhibitors (when causing hypophysitis)	• Central hypothyroidism (↓ TSH production)
	• Others: Glucocorticoids, dopamine agonists, somastostatin analogs, metformin	• Suppress TSH and normal free thyroxine (FT4), because of decreased TSH release
Affecting thyroid hormone synthesis or release	• Iodolactones and iodoaldehydes, iodinated contrast agents, high iodine content medications	• Primary hypothyroidism (Wolff-Chaikoff effect) or thyrotoxicosis (Jod-Basedow phenomenon) if preexisting autonomy
	• Amiodarone (see also hyperthyroidism)	
	• Lithium	• ↓ Thyroid hormone release: Lithium causes goiter (50%) and hypothyroidism (17%)

Enhance thyroid autoimmunity	• Immune checkpoint inhibitors (e.g., CTL-4, PD-1)	• Painless thyroiditis (50% exhibit positive antithyroid antibodies): Transient thyrotoxicosis followed by persistent and/or irreversible hypothyroidism
	• Interleukin-2 and interferon alpha	• Thyroid dysfunction (15%–50%); varying degrees of hypothyroidism often preceded by thyrotoxicosis due to thyroiditis, often positive antithyroid antibodies
	• Alemtuzumab (for multiple sclerosis)	• Thyroid dysfunction in 41%; Graves' disease in 71% of affected
	• After active antiretroviral therapy for HIV infection	• Graves' disease
Destructive thyroiditis	• Amiodarone (see also hyperthyroidism)	
	• Multikinase inhibitors (sunitinib)	• Thyroiditis with hypothyroidism (14%–25%) transient or permanent

Affecting protein binding of thyroid hormone	• Oral estrogens, selective estrogen-receptor modulators, methadone, heroin, mitotane, and fluorouracil	• ↑ Thyroxine-binding-globulin (TBG): Elevated total T4 and T3 but normal free thyroxine (FT4) and TSH
	• Androgens, glucocorticoids, niacin	• ↓ TBG: Decreased total T4 and T3 with normal FT4 and TSH
	• Phenytoin* and carbamazepine,* salsalate,* and some nonsteroidal antiinflammatory drugs, high-dose furosemide, heparin preparations†	• Drug-induced displacement of thyroid hormone from binding proteins: (1) all exhibit normal TSH. (2) *Low FT4 trend, †high FT4 trend
Affecting thyroid hormone activation, metabolism, and excretion	• Amiodarone, glucocorticoids (dexamethasone), propranolol (high doses), iodinated contrast agents, propylthiouracil (PTU)	• ↓ Conversion of T4–T3
	• Drugs inducing glucuronidation (antiepileptic agents, rifampin and others) and tyrosine kinase inhibitors (sorafenib)	• ↑ Thyroid hormone metabolism; FT4 dose increase may be needed

Drug effect	Compound	Condition/test results
thyroid hormone preparations	inhibitors, ferrous sulfate, calcium carbonate, aluminum hydroxide, sucralfate, raloxifene	
Causing abnormal thyroid tests in euthyroid patients	• Biotin	The direction and degree of interference depend on the assay platform: Frequently, a falsely ↓ TSH, and ↑ FT4 level, with spuriously positive results of TSH-receptor antibodies
	• Amiodarone, heparin, phenytoin, carbamazepine, and salsalate	• See earlier and hyperthyroidism

CLINICAL MANIFESTATIONS

- Symptoms
- Clinical hypothyroidism has an insidious onset; symptoms and signs are more difficult to identify than in young adults, given their similarity to those of "old age" or the common comorbidities associated with age (see next pictures)
- Most common symptoms
  - Generalized weakness and fatigue or lethargy
  - Neurological symptoms: Bradypsychia, excessive sleepiness
  - Confusion with psychiatric disorders: Depression, delirium, or paranoid ideation
  - Others: Ataxia, hypogeusia or ageusia, hearing impairment
  - Acute depression of mental state can be precipitated by infections, trauma, hypothermia, or administration of sedatives and narcotics
  - Other common symptoms: Cold intolerance, weight gain from edema/myxedema,
  - paresthesias, muscle cramps, constipation

Signs

- More frequent signs in older age are: Bradycardia, pallor, dry skin, thin hair, deep and rough voice, dysarthria, delayed relaxation of tendon reflexes (specific sign, if present), and changes in mental state
- Neuropsychological tests with low scores
- Severity in signs can be exacerbated by age-related comorbidities
- Atrophic form of autoimmune thyroiditis is the commonest etiology
- Myocardial involvement: Decreased cardiac output, possible cardiomegaly due to myxedematous infiltration, and symptoms of ischemic heart disease
- Peripheral edema because of: Diminished cardiac output, decreased GFR, and renal retention of sodium and water
- Pericardial effusion is infrequent

laboratory findings:

- Elevated serum Cr and CK (musculoskeletal origin);
- hyponatremia (multifactorial and SIADH); normocytic or macrocytic anemia (15%) and
- hypercholesterolemia

Euthyroid sick syndrome:

- Nonthyroidal illnesses, more common in the elderly, may cause changes in thyroid hormones and TSH
- Severe illness alters the transport (protein binding) and metabolism (deiodination) of

thyroid hormones, and the regulation of TSH production (by pro-inflammatory cytokines)

Consequences:

- • Decreased serum concentrations of total (and to a lesser extent free) T4 and T3; normal

or decreased TSH

- • Clinical euthyroidism which does not require thyroxine treatment

DIAGNOSIS: OTHER COMPLEMENTARY TESTS

- Thyroid ultrasound:
  - (1) Indicated only if there are palpable nodules;
  - (2) hetero or hypoechoic in autoimmune thyroiditis;
  - (3) autoimmune thyroid nodules are usually solid and/or hyperechoic
- Thyroid fine-needle aspiration biopsy (FNA): If there are nodule/s or diagnostic doubts as indicated
- Autoimmunity screening needed: Determine B12, ferritin, antitransglutaminase antibodies ,primary autoimmune adrenal insufficiency if clinical suspicion byinitial measurements of basal cortisol and ACTH

- If low B12 or anemia: Antiintrinsic factor, antiparietal cell antibodies
- Hematologic tests: Pernicious anemia (12%) or increased mean corpuscular volume; leukopenia or thrombocytopenia of autoimmune origin
- Cardiovascular: (1) Chest X-ray: cardiomegaly, pleural effusion; (2) EKG: low voltage, bradycardia, flattened ST and T depression (nonspecific);
- echocardiogram: diminished ejection fraction and pericardial effusion
- Other: Hypercholesterolemia and elevated Other: Hypercholesterolemia and elevated LDH, GGT, or CPK, which are normalized with LT4 therapy

ERLY:

- **Standard care of therapy:** Levothyroxine monotherapy (strong recommendation)
  - **Goals of therapy:** Resolution of symptoms and signs, normal TSH, and avoid overtreatment
  - **Dose:** Start with low dose, and titrate slowly. 1.6 μg/kg in patients with autoimmune etiology and 2.1 μg/kg in those with surgical hypothyroidism. Requirements in the elderly patient may be lower
  - **Considerations:** (1) Chronic comorbidities (e.g., coronary artery disease) must be considered in deciding the rate of dosage increase; (2) in patients on higher than expected doses, GI disorder should be ruled out (*Helicobacter pylori* or atrophic gastritis, celiac disease)
- **Drug interactions:** Initiation or discontinuation of estrogens, androgens, tyrosine kinase inhibitors, phenobarbital, phenytoin, carbamazepine, rifampin, or sertraline may alter dose requirements
- **TSH recheck for dose adjustment:** Every 4–6 weeks. Higher TSH targets are appropriate (4–6 mU/L) in persons older than 70–80 years
- **Incapacitated elderly:** Consider once a week dose under supervision (guardian or nurse)

Treatment and follow-up recommendations”

- • Initial total dose calculation: 1.6μg/kg/day ,L-T4 intake:
- (1) Fasting (30–60 min before eating) only with water;
- (2) without taking fiber or other medications, 4 h before or after if possible;
- (3) different brands are not necessarily bio-equivalent, if the brand is changed dose should be reassessed according to TSH, 6weeks later;
- (4) the same dose per day is better than different doses each day
- Older patients often need lower doses, because of the decreases in metabolic clearance of T4 (longer half-life) and lean body mass (better predictor).
- Dose also is influenced by other medications being used and comorbidities
- Maintenance doses are usually 20–40μg/day less than in younger people (20% less per kg of body weight/day)
- Recommended start 25–50μg/day; without evidence of ischemic heart disease, 50μg/day; otherwise, start with 12.5–25μg/day

- starting LT4 at low doses and slowly increasing, seems to minimize the risks of developing or exacerbating ischemic heart disease, HF, and arrhythmias
- Dosage can be increased by 12.5–25µg/day every 4–6weeks until TSH normalization after CV tolerance has been established.
- LT4 by TSH adjustment at 6 weeks: Once the dose is established, keep TSH in normal range, but higher than in younger population (1–4 mU/L)
- available evidence suggests raising serum TSH target to 4–6mU/L in people over 70–80 years of age

Increased T4 Requirements[22]

- Weight gain
- Drugs that increase the catabolism of thyroid hormones[27]
  - Barbiturates, diphenylhydantoin, carbamazepine
  - Serotonin reuptake inhibitors
  - Tricyclic antidepressants
  - Rifampin
- Drugs that interfere with thyroid hormones absorption[27]
  - Iron supplements
  - Tamoxifen, raloxifene
  - Cholestyramine, colestipol
  - Antacids and sucralfate
  - Calcium carbonate
  - Sertraline
- Malabsorption and small bowel syndromes
- Decreased acid secretion
  - Autoimmune gastritis with antiparietal cell antibodies (17% more)[28]
  - Proton pump inhibitors
- Dietary fiber ingestion
- Food intake (10%–20% more)
- Nephrotic Syndrome (by increased renal excretion)
- Androgen therapy (slight increase)
- Progressive worsening of thyroid function

SPECIAL CONSIDERATIONS

- • Myxedema coma
  - • Almost exclusively in older people; diagnosis and early initiation of treatment is essential, otherwise mortality is as high as 40%–50%
- • Possible interference with LT4 by other drugs
- • LT4 replacement and Ischemic Cardiomyopathy (IC)
- • Some older hypothyroid patients with IC do not tolerate a full replacement dose, even with the addition of propranolol
- • Up to 46% of patients surveyed rated the symptom control as inadequate for both Diseases
- • Treatment nonadherence
  - • Both for cognitive and/or care limitations and for the inconsistent patient behavior
- • Acceptable control has been reported by giving the entire weekly dose just one or two days per week
- • Uncertain diagnosis: To assess if LT4 can be withdrawn, the dose can be halved and TSH repeated every 6weeks

Overreplacement Risks

- Do not treat based only on symptoms, without biochemical confirmation
- Hyper or hypo-replacement with LT4 is common[10,13,18,32]:
  - Normal TSH (0.4–4 mU/L): 38%, 47%, and 60%
  - Low TSH (<0.1–0.4 mU/L): 21% and 58%
  - High TSH (>4 mU/L): 18% and 37%
- Especially common in >65 years[33]:
  - Normal TSH 43%
  - *Low TSH 41%*
  - High TSH 16%
- Increased adverse CV risk
- Men and women ≥60 years old: Risk of arrhythmias (TSH < 0.1)
- Women >50 (postmenopausal): Risk of osteoporosis and increased number of fractures (TSH < 0.03)[34]
- Increased blood pressure
- Cardiomyopathy
- Long-term myocardial hypertrophy
- Ischemic cardiopathy

Parameters to Consider in Optimizing Therapy

- Ultrasound: Thyroid volume, presence of nodules, or heterogeneity
- Age: Over or under age 65
- Body mass index (BMI)
- Presence of heart failure
- Risk of dysrhythmias
- Atherosclerosis
- Metabolic syndrome
- Bone: Risk of osteoporosis and/or fractures
- Gender[35]
- Presence of positive antithyroid antibodies
- Chronic iodine intake
- Thyroglobulin (TG) $>$ 20 ng/mL (suspect low iodine intake)
- Depressive mood
- Multinodular goiter
- Presence of nonthyroidal disease
- Hypertension
- Hypercholesterolemia

- HYPOTHYROIDISM IN THE ELDERLY:
  - MYXEDEMA COMA
- Caused by Severe and Decompensated Hypothyroidism

- **Triggers**
  - Almost exclusively in older patients
  - Hypothermia: Most common in the winter; less commonly, in excessively air conditioning environments
  - Respiratory failure
  - Infections
  - Trauma
  - Use of sedatives and narcotics
- **Clinical**
  - Severe weakness
  - Bradypnea and respiratory failure
  - Bradycardia, hypotension
  - Ileus
  - Hypothermia, stupor and coma
  - Hyponatremia, hypoglycemia

ICU Management

- **General care**
  - Hydration
  - Monitoring
  - Mechanical ventilation
  - Search and treat trigger
- **I.V. levothyroxine**
  - Initial 3 μg/kg (+T3 10 μg)

DIAGNOSTIC CRITERIA
Subclinical hypothyroidism: Follow-up recommendations"

- • High TSH (>4–5mU/L in most labs) with normal FT4
- • It has been classified in 2 grades40
  - • Grade I: TSH from the normal range to <10 mU/L (90% of patients)
  - • Grade II: TSH equal or greater than 10 mU/L (10% of patients)
- • In those over 65 years, values from 6 to 8mU/L are considered normal (6.9mU/L average)
- • It must be persistent
- • TSH normalization in 2years in patients >65 years: (1) 46% in grade I; (2) 7% in grade 2; 48% if negative anti-TPO antibodies
- • Normalization most likely when: (1) TSH<10mU/L; (2) negative thyroid antibodies
- • Repeat TSH at 3 months. If TSH>15, repeat it in 1–2 weeks with FT4

Elevated serum TSH and normal serum free T4

Subclinical hypothyroidism with mild thyroid failure

- Hashimoto's thyroiditis
- Insufficient LT4 replacement for primary hypothyroidism
- Following thyroid lobectomy (see etiology of hypothyroidism)
- Following antithyroid drug or radioiodine therapy for hyperthyroidism (see etiology of hypothyroidism)
- Following external beam radiotherapy to the head and neck (more than 25 Gy)
- Infiltrative disorders (amyloidosis, Riedel thyroiditis, sarcoidosis, hemochromatosis)
- Following an episode of subacute thyroiditis (usually transient)
- Drug induced, especially in patients with underlying lymphocytic thyroiditis
  - Lithium carbonate therapy
  - Iodides and organic iodine compounds (amiodarone)
  - Interferon alfa therapy
- Tyrosine kinase inhibitors (15%–42% of patients present with elevated TSH)
- Immune check point inhibitors (nivolumab, pembrolizumab, atezolizumab)

Physiological transient rise in serum TSH

- Recovery phase from severe nonthyroidal illness
- Recovery phase from various forms of thyroiditis
- Following withdrawal of chronic LT4 therapy in a euthyroid individual
- Iodine deficiency (reversible with iodine supplementation)
- Seasonal (winter-time) increase in serum TSH

CLINICAL RELEVANCE

- • About 10% of the population is affected; subclinical hypothyroidism is more prevalent in women and in patients over 65 years of age
- • Patients are often asymptomatic if TSH is ≤10mU/L
- • No specific symptoms: Asthenia, depression, constipation; these often do not differ from those in elderly persons who have normal TSH
- • No significant relationships have been shown in the healthy elderly between elevated TSH (>5.51 or >4.8 mU/L) with normal FT4, and physical dysfunction, cognitive impairment, depression, or anxiety

CV disease or mortality

- • There is no clear evidence that grade I subclinical hypothyroidism is associated with increased CV risk
- • Metaanalysis : TSH>10mU/L was associated with increased coronary risk and CV mortality
- • HF is more common with TSH>8–10mU/L
- • CHF in a data analysis of 6 prospective studies
  - • TSH 10–19.9: Significant increase in congestive heart failure (CHF) episodes
  - • TSH 7–9.9: Non significant in episodes
  - • TSH 4.5–6.9 mU/L: No increase in episodes

- **Dyslipidemia has been observed** — elevation of LDL cholesterol and triglycerides—in patients with grade 2 subclinical hypothyroidism, particularly in cigarette smokers or those with insulin resistance

TREATMENT WITH LEVOTHYROXINE

- **• TSH 4.5–10mU/L**
- • 2%–4% of patients per year evolve to clinical hypothyroidism, depending on the positivity of anti-TPO antibodies
- LT4 therapy in older age is avoided, except in some patients with depressive disorders or when anti-TPO antibodies are positive
- • Some authors consider LT4 therapy in patients older than 65 years with TSH from
- 7 to 9.9 mU/L, who may have an associated increased risk for stroke and coronary artery disease mortality

TSH>10mU/L

- • There is evidence of benefit of treatment because progression to overt hypothyroidism is lessened, LDL cholesterol decreases, symptoms improve, and goiter size is reduced
- • Treatment is also recommended as an attempt to reduce the risk of HF and mortality due to coronary events

LT4 Dosage

- • In older patients on LT4 therapy, serum TSH should be maintained at higher levels than in young people.
- • Usual dose is 25–75 µg/day, which is less than in patients with overt hypothyroidism
- • In old age, LT4 is started with doses of 12.5–25 µg/day
- • Slow increase in the elderly, every 2–4weeks, especially if there is CV disease
- • When FT4 is normal, it is not necessary to delay any non thyroidal surgery
- • Overdosing should be avoided

HYPERTHYROIDISM IN THE ELDERLY

PREVALENCE AND ETIOLOGY

- 36%–40% of older patients taking LT4 have low TSH; this frequency reached 50% in one community study
- • it is similar to that in young adults (0.4%)
- • Of all patients with hyperthyroidism, 15%–20% are >60years

- Most common etiology in older patients is hyperfunctional or toxic MNG

(50%; excluding those on LT4)

- • Even more common in areas with iodine deficiency
- • The second most common etiology is Graves' disease, which is associated with a higher prevalence of severe thyroid ophthalmopathy in patients older than 40years

Less common etiologies include

- • Toxic adenoma: Uncommon in elderly
- • Subacute or silent thyroiditis: Less common in elderly than in young adults. The
- clinical course is similar in both age groups
- • Amiodarone: More common cause of hyperthyroidism in the elderly than in younger patients; iodine contrast and radioiodine administration are rare causes in old age,
- although the elderly are more susceptible to developing organic iodine hyperthyroidism

DRUG	MECHANISM	START AFTER USE OF THE DRUG	TREATMENT
Amiodarone-induced thyrotoxicosis (AIT)	Iodine-induced (AIT type 1)	Months to years	• Support measures • Thionamides; perchlorate • Surgery
	Thyroiditis (AIT type 2)	Usual >1 year	• Support measures • Glucocorticoids • Surgery, exceptionally
Iodine contrast agents	Underlying thyroid autonomy More frequent use in elderly	Weeks to months	Thionamides
Radioiodine (early phase)	Destruction	1–4 weeks	Observation; if severe glucocorticoids
Radioiodine in MNG (late phase)	Development of autoimmune hyperthyroidism	3–6 months	• Thionamides • Repeat radioiodine • Surgery

- The development of thyroid nodules is age related and more frequent process in women
- • Thyroid nodules are detected in autopsies in 90% of women and 50% of men >70years old
- • Ultrasound detected nodules occur in 50% of women >50 years old

DIFFERENTIATING CLINICAL MANIFESTATIONS

- • Different presentation versus that in the young, can be latent or atypical
- • Apathetic hyperthyroidism: Weight loss, depression, and agitation are more common, with no symptoms of sympathetic activation (tremor, hyperactivity, sweating)
- • Other common symptoms are: Fatigue, anorexia, apathy, cognitive decline, and muscle weakness
- • Nonspecific presentation in an older person: Consider ruling out a diagnosis of hyperthyroidism in patients presenting with weakness, persistent vomiting, hypercalcemia, or worsening osteoporosis

- • In addition to the classic tachycardia and systolic hypertension, atrial fibrillation is more prevalent and severe
- • Cardiac and cerebrovascular events, especially ischemic, hypertensive, valvular, HF, and cerebral embolism, are associated with increased morbidity and mortality
- • Elderly patients in the above settings should undergo more frequent thyroid function and cardiovascular testing

DIAGNOSTIC CHARACTERISTICS

- • diagnosis is based, as in the young patient, on elevated free T4 (or total T3) and low TSH
- • Obtaining total T3 (standardized) if the TSH is low and T4 is normal. Possibilities:
- • Elevated T3 (T3 hyperthyroidism)
- • Sometimes occurs in MNG, toxic adenoma, and in Graves' disease
- • Serum T3 levels helps to differentiate between hyperthyroidism (high-normal T3) and functional impairment of a nonthyroid disease (low-normal T3)
- • An undetectable TSH (0.01 mU/L) is often due to true hyperthyroidism

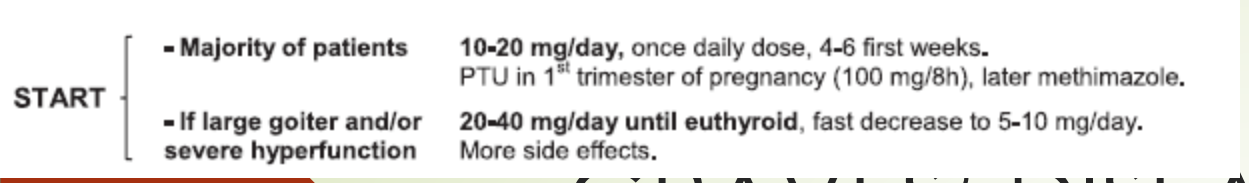
- **• Normal T3 and T4 with low TSH—subclinical hyperthyroidism—is more common in the elderly**
- • Thyroid function tests can be altered by many systemic diseases in elderly patients
  - • Subnormal TSH: High doses of glucocorticoids, dopamine and its agonists, heparin
  - • High FT4 (increased serum T4/T3 ratio) by lower peripheral conversion from T4 to T3: Amiodarone and iodine contrast agents; propranolol and glucocorticoids
  - Malnutrition and postoperative stage, can also increase serum T4/T3 ratio
- Other diagnostic tests: Antithyroid antibodies, imaging tests (ultrasonography, scintigraphy, and CT) have the same indications as in young adults

When to treat[74,88,89]

- **If TSH < 0.1 mU/L**. Repeat TSH 3–6 months later, confirm persistence for more than 3–6 months and diagnose cause. Treatment indicated in
  - All those ≥65 years old
  - Postmenopausal women not taking estrogens or bisphosphonates
  - Patients with cardiac risk factors, cardiac disease, or osteoporosis
  - Patients with symptoms of hyperthyroidism
- **If TSH 0.4–0.1 mU/L.** Repeat TSH 3–6 months later and consider treatment in:
  - All those ≥65 years old
  - Patients: (1) With symptoms of hyperthyroidism; (2) Postmenopausal women not taking estrogen therapy or bisphosphonates; (3) With osteoporosis; (4) With cardiac disease
  - Those <65 years without signs or symptoms: Only follow-up

How to treat[74,88,89]

- Individualize treatment based on etiology and follow the same principles as for therapy of clinical hyperthyroidism
- Some hyperthyroidism cases are transient and don't need therapy
- Objective: To achieve euthyroidism with normal TSH



GRAVES' DISEASE TREATMENT SCHEME

- • BEFORE STARTING: Complete blood count (CBC), liver function tests (LFT) and bilirubin.
- No methimazole if < 500 neutrophils/mm3 or transaminases > 5 fold the normal range.
- • **METHIMAZOLE DOSE:**

FOLLOW UP AND MAINTANANCE DOSE:

- • re-measure FT4/TSH in 4-weeks to lower dose to 5-10 mg/day, depending on response.
- Lower dose if FT4 lower than normal even if TSH is low.
- Until normalization of thyroid function → re-measure every 4-6 weeks: CBC,
- FT4, TSH and LFT. If low TSH, the total T3 is useful.
- Normal thyroid function → re-measure every 2-3 months: CBC, FT4, TSH and LFT.
- • DURATION: 12-18 MONTHS.
- **side effect:**
  - Hepatotoxicity (Transaminitis or cholestasis),
  - abdominal discomfort, arthralgia, fever,
  - pharyngitis (rule out agranulocytosis).

pharyngitis (rule out agranulocytosis).

2nd LINE

I^{131}

- **SIDE EFFECTS BY THIONAMIDES: Pruritus or rash without response to antihistamines or other**
- **OTHER**
  - Recurrence of hyperthyroidism or unresponsiveness to treatment with methimazole.
  - Previous thyroid surgery or external radiation of the neck.
  - Heart failure (high doses of therapy) or comorbidities associated with surgical risk.
  - Noncompliance with thionamides.
  - If indication for surgery but no suspicion of malignancy and no access to an expert surgeon.
  - (Normalization of thyroid function 6 months prior to pregnancy)

PREPARATION

- METHIMAZOLE: Not always needed. Treat up to normal FT4 in: very symptomatic patients, severe hyperthyroidism (FT4> 2 fold normal), > 65 years or with comorbidities with risk of complications (cardiovascular disease, renal failure, infections, trauma, uncontrolled diabetes, cerebrovascular or pulmonary diseases).
- • If previous treatment with methimazole: Suspend 3-5 days before. Consider to re-start 3 days later.
- • Continue with symptomatic beta blockers. Beta blocker after I131 until normal FT4 and total T3.
- • Avoid iodized salt.
- `DOSE: 10-20 mCi or 150-200 µCi/g of thyroid tissue.
- FOLLOW UP POST RADIOIODINE THERAPY: FT4 and total T3 in 4 to 8 weeks (TSH takes longer to normalize)

- ***3rd LINE***

SURGERY

- **Methimazole intolerance**
- **Moderate to severe active orbitopathy**
- **Large thyroid (> 80 gr)**
- **Other**
  - Patient preferences: Fear of I131 or drugs or desire for faster control
  - Symptomatic compression (dysphagia, respiratory)
  - Coexisting hyperparathyroidism
  - Low iodine uptake
  - Malignant or suspicious nodules
  - Large non-functioning nodules
  - (Pregnancy planning)

- Expert surgical team is essential
- Total thyroidectomy (or intentionally total) or subtotal (leaving 4 to 7 g of thyroid)

PREPARATION

- Methimazole until FT4 is normalized.
- Lugol: 5-7 drops/TID, 10 days prior to surgery (if not pregnant).
- Continue with beta blockers until surgery.

IMMEDIATE POSTOPERATORY

- Calcemia 6 and 12 h after intervention. Also recommended iPTH.
- Consider use of oral prophylactic calcium in the immediate postoperative period.
- If persistent hypocalcemia: Calcemia and iPTH 1-2 weeks after discharge.
- No systematic use of oral calcium/vitamin D at discharge
- Stop antithyroid and beta blockers.
- **Start Levothyroxine: 1.7 mcg / kg / day (if total thyroidectomy). Repeat TSH in 6-8 weeks**

- Endocrinology of Aging: Clinical Aspects in Diagrams and Images.
- https://doi.org/10.1016/B978-0-12-819667-0.00006-8 191
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Thanks for attention