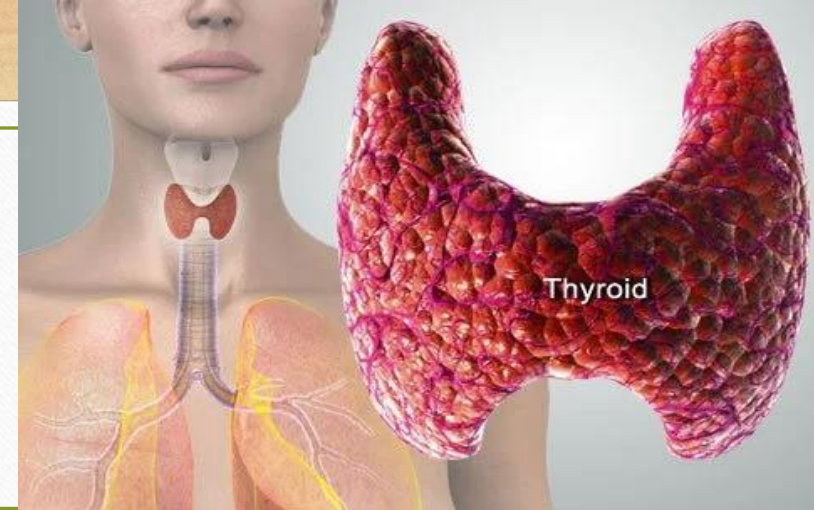


Overview of Hypothyroidism

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Agenda



- Definition
- Symptoms and Signs
- Who need to treat ?
- Standard Replacement Therapy
- Patient-Appropriate TSH Goals
- Goal of treatment
- L-T4 dose
- Subclinical Hypothyroidism
- TSH responses
- Adjustment of Levothyroxine Therapy
- Avoidance of Iatrogenic Thyroid Disease
- Levothyroxine Absorption
- L-T3 alone or Combination T4 and T3 therapy

Definition



- ❑ **Overt primary hypothyroidism:** high TSH and low fT4
- ❑ **Subclinical hypothyroidism :**high TSH and normal fT4
- ❑ **Central hypothyroidism:** low fT4 and not appropriately elevated TSH
TSH may be low, normal, or even slightly elevated (up to approximately 10 mU/L)



Definition(cont.)

- The definition of an abnormal high TSH level is controversial.
- More acceptable value is approximately 4.5 to 5.0 mU/L.
- **Elderly individuals** may have serum TSH levels above the reference range for the general population.
- In the NHANES III study, the TSH upper limit of normal for participants 80 years and older with no other evidence of thyroid disease was **7.5 mU/L.**

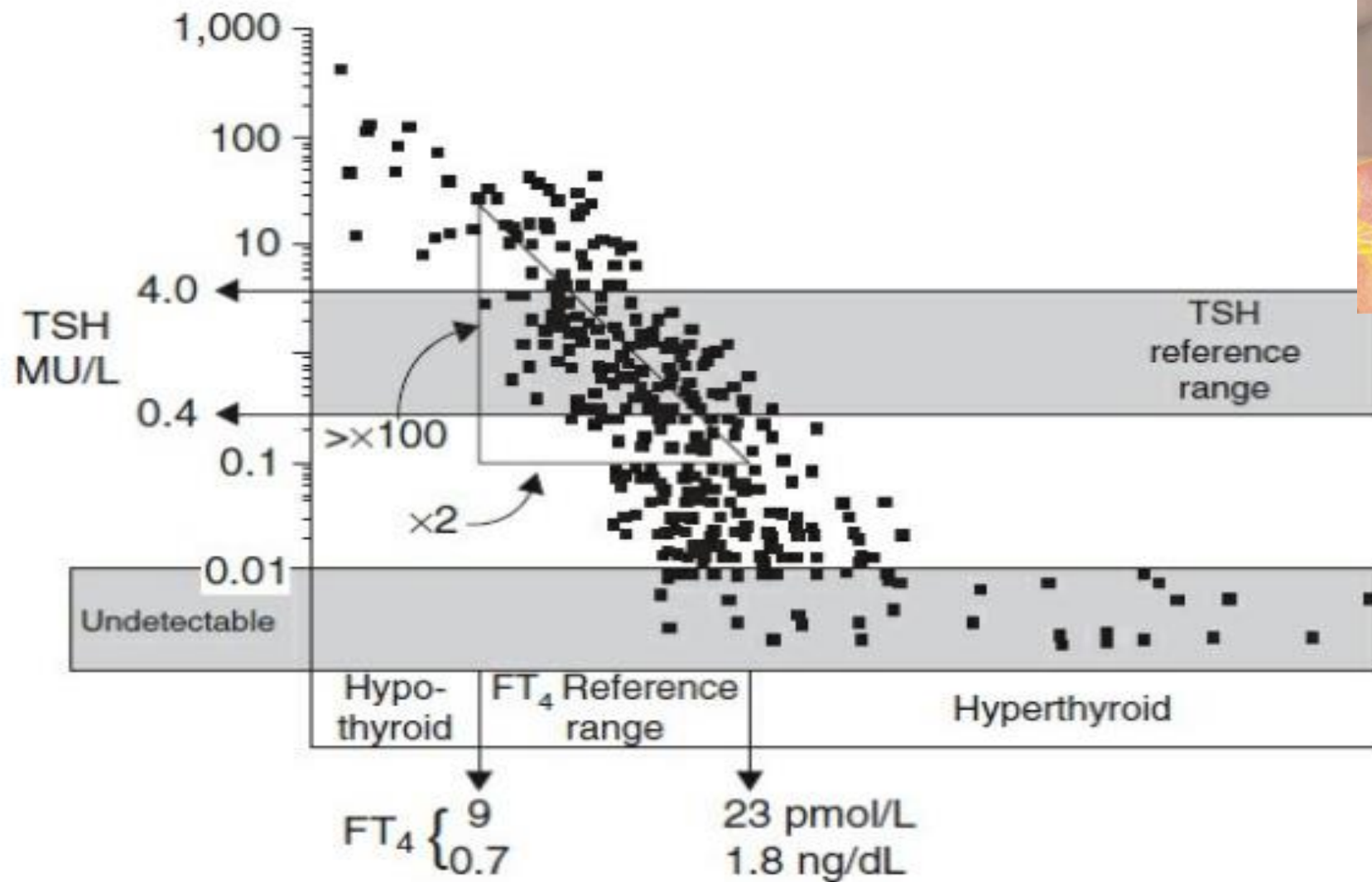


FIGURE 17-2. The log-linear relationship between thyrotropin (TSH) and free thyroxine (FT₄) concentrations in individuals with stable thyroid status and normal hypothalamic–pituitary–thyroid function. (Adapted from reference (2, 28) and reprinted with permission.)

Symptoms and signs



- Many of symptoms are **very nonspecific**.
- Symptoms may be **minimal or absent** in some patients with biochemically significant disease and can be numerous in patients with only mild disease.
- Elderly persons generally experience fewer classic symptoms and signs and prominent features include **fatigue and weakness**.

TABLE 65.5 Clinical Features of Hypothyroidism

Children

Learning disabilities
Mental retardation
Short stature
Delayed bone age
Delayed puberty

Adults

Fatigue
Cold intolerance
Weight gain
Constipation
Menstrual irregularities
Dry, coarse, cold skin
Periorbital and peripheral edema
Delayed reflexes
Bradycardia
Arthralgias, myalgias



Who need to treat ?



All patients with overt hypothyroidism (primary or central) require treatment (regardless of symptoms)

unless

the hypothyroidism is transient (as after painless thyroiditis or subacute thyroiditis)

or

reversible (due to a drug that can be discontinued)

- Thyroid hormone should not be prescribed to **biochemically euthyroid individuals with nonspecific symptoms** (fatigue, obesity, depression, urticaria) 1/++0

Standard Replacement Therapy



- **LT₄** is a convenient therapy for hypothyroidism.
- **Absorption** after oral administration is acceptable and the **half-life of a week** allows once daily dosing.
- LT₄, as the sodium salt of thyroxine (T₄), is actually a **prohormone** and is converted into the active triiodothyronine (T₃).

L-T4 dose



- In those with minimal residual thyroid function a full replacement dose is approximately **1.6 mcg/kg/day**.
- In patients known to have ischemic heart disease, treatment should be initiated with lower doses of LT4 **such as 25 mcg daily** .
- In other patients at risk for coronary artery disease, but without documentation of such disease, a conservative starting dose of approximately **50 mcg per day may be advisable**.



- This caution would apply to patients who are **elderly or who have had long-standing severe hypothyroidism**.
- If a **patient has both hypothyroidism and suspected or documented adrenal insufficiency**, cortisol replacement should be started concurrently with LT4.
- **Pregnant** patients should always be started on a full replacement dose.

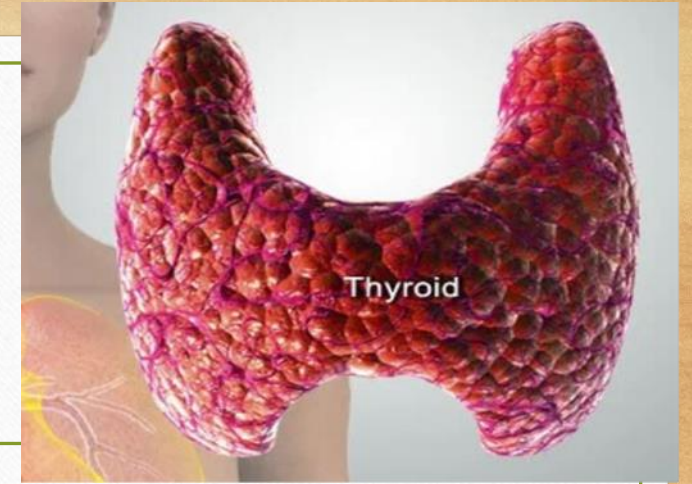
LT4 Dosing in Hypothyroid Patients(cont.)

Patients status	L-T4 Dosage
Neonate	10-15 µg/kg/d
1-3 years	4-6 µg/kg/d,
3-10 years	3-5 µg/kg/d,
10-16 years	2-4 µg/kg/d
adult	1.6 µg/kg/d
elderly	1-1.2 µg/kg/d

Subclinical Hypothyroidism



- There are no universally accepted recommendations for the management of subclinical hypothyroidism, but LT₄ is recommended if the patient is a woman who wishes to conceive or is pregnant or when TSH levels are >10 mIU/L.
- Most other patients can simply be monitored annually.



-
- A trial of treatment may be considered **when young or middle-aged patients have symptoms of hypothyroidism or risk of heart disease.**
 - No evidence it is beneficial to treat persons aged 65 years or older.



-
- It is important to confirm that any elevation of TSH is sustained over a 3-month period before treatment is given.
 - Treatment is administered by starting with a low dose of LT₄ (25–50 $\mu\text{g}/\text{d}$) with the goal of normalizing TSH.

③ Treatment initiation considerations

		Thyrotropin level, mU/L	Patients <65 years	Patients ≥65 years
		0.4-4.4	Normal thyrotropin reference range	
Subclinical hypothyroidism	Grade 1	4.5-6.9	<ul style="list-style-type: none"> • Measure thyroid peroxidase (TPO) antibodies • Annual follow-up thyrotropin measurement of asymptomatic patients • Consider treatment with levothyroxine (LT₄) in patients with <ul style="list-style-type: none"> Multiple symptoms of hypothyroidism Positive TPO antibodies Progressively increasing thyrotropin levels A plan for pregnancy Goiter 	Treatment is not recommended
	Grade 2	7.0-9.9	Treat with LT ₄ to reduce risk of fatal stroke and coronary heart disease (CHD) mortality ^a	Consider treatment with LT ₄ to reduce risk of CHD mortality ^a
		≥10.0	Treat with LT ₄ to reduce risk of progression to overt hypothyroidism, heart failure, CHD events, and CHD mortality ^a	

④ Treatment follow-up

- If treatment is initiated, measure thyrotropin level in 6 weeks and adjust LT₄ dose if necessary.
- Once target thyrotropin level is reached, perform annual measurement to confirm that it remains within the target range.

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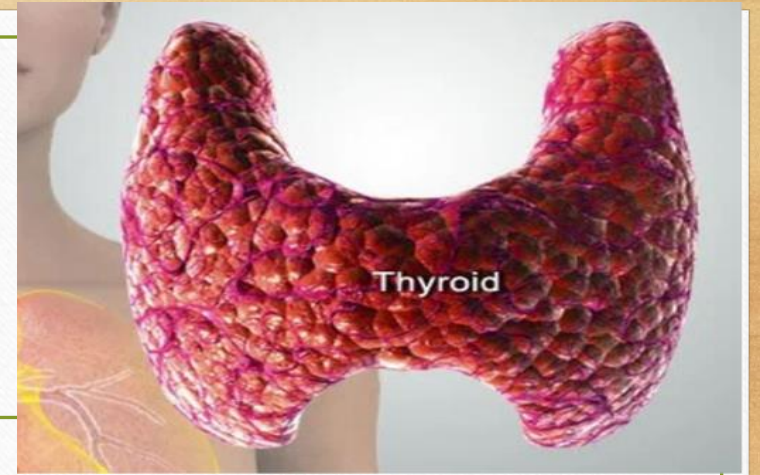
Patient-Appropriate TSH Goals



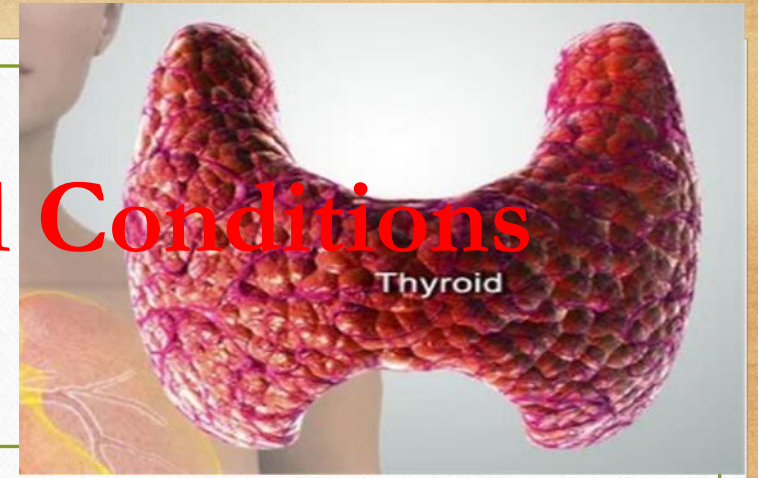
- The goal of treatment being a normal TSH, ideally in the **lower half of the reference range** (**FT4 in secondary hypothyroidism**).

Patient Age:

For example, an increase in LT4 dose may be inappropriate for a 70 year old with a serum TSH of 5.5 mIU/L, but might be the best approach for an individual who is 35 years old.



Co-existent Physiologic or Medical Conditions



Women being treated for hypothyroidism typically require a 20% to 30% increase in their LT4 dose early in the **first trimester of pregnancy.**

Differentiated Thyroid Cancer :

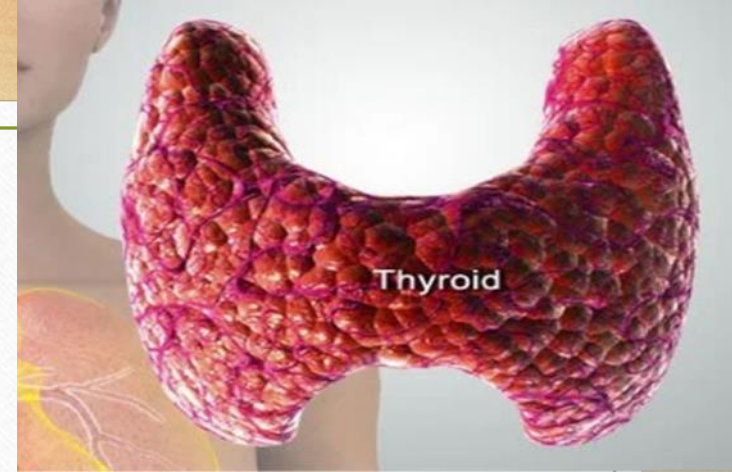
A subgroup of patients who are intentionally kept with TSH values below the normal range are those with **intermediate or high-risk differentiated thyroid.**

Individuals with Central Hypothyroidism



- FT4 levels be kept in the **upper half of the normal** range.
- Slightly lower FT4 levels, perhaps in the midnormal range, has been suggested for frail **or older individuals**.

TSH responses



- TSH responses are gradual and should be measured about **2 months after instituting treatment or after any subsequent change in LT4 dosage.**
- The clinical effects of LT4 replacement are slow to appear. Patients may not experience full relief from symptoms **until 3–6 months** after normal TSH levels are restored.

Adjustment of Levothyroxine Therapy

- Adjustment of LT4 dosage is made in 12.5- or 25- μ g increments if the TSH is high; decrements of the same magnitude should be made if the TSH is suppressed.
- About 10–15% of patients may have persistent symptoms despite restoration of euthyroidism with LT4 for reasons that remain unclear.

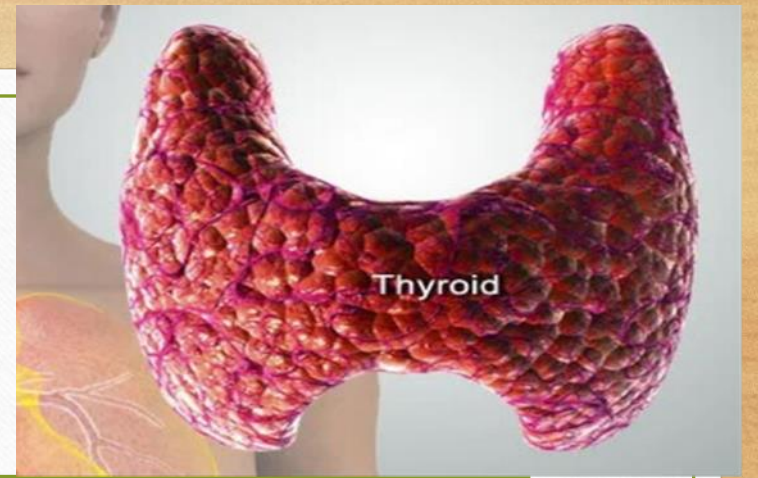
Avoidance of Iatrogenic Thyroid Disease

- Avoidance of long-term iatrogenic hypothyroidism or hyperthyroidism is desirable in all patients treated for hypothyroidism.

Levothyroxine Absorption



- The absorption of an orally administered tablet of **LT4** is about **70% to 80%** under optimum conditions, which **is when the patient is fasting**.
- **When LT4 is co-administered with food there is reduced absorption of 10% to 40%** compared with absorption in the fasting state, possibly due to the decreased acidity associated with the buffering effect of food
- The factors affecting LT4 absorption include various medical disorders, many medications, and food and drink



- In patients of normal body weight who are taking $\geq 200 \mu\text{g}$ of LT_4 per d, an elevated TSH level is often a sign of poor adherence to treatment.
- This is also the likely explanation for fluctuating TSH levels, despite a constant LT_4 dosage.

TABLE 13.3**Conditions That Alter Levothyroxine Requirements****Increased Levothyroxine Requirements****Pregnancy*****Gastrointestinal Disorders***

Mucosal diseases of the small bowel (e.g., sprue)
After jejunioileal bypass and small bowel resection
Impaired gastric acid secretion (e.g., atrophic gastritis)
Diabetic diarrhea

Therapy With Certain Pharmacologic Agents***Drugs That Interfere With Levothyroxine Absorption***

Cholestyramine
Sucralfate
Aluminum hydroxide
Calcium carbonate
Ferrous sulfate

Drugs That Increase the Cytochrome P450 Enzyme (CYP3A4)

Rifampin
Carbamazepine
Estrogen
Phenytoin
Sertraline
? Statins

Drugs That Block T_4 to T_3 Conversion

Amiodarone

Conditions That May Block Deiodinase Synthesis

Selenium deficiency
Cirrhosis

Decreased Levothyroxine Requirements

Aging (≥ 65 years)
Androgen therapy in women



L-T3 alone or Combination T4 and T3 therapy

- The use of LT4 combined with liothyronine (triiodothyronine, T3) has been investigated, but benefit has not been confirmed in prospective studies.
- There is no place for liothyronine alone as long-term replacement, because the short half-life necessitates three or four daily doses and is associated with fluctuating T3 levels.

Summary



- ❑ **LT4** should be the **first choice** in replacement therapy for all hypothyroid patients.
- ❑ Thyroid hormone **should not be prescribed** to biochemically euthyroid individuals with nonspecific symptoms (**fatigue, obesity, depression, urticaria**).
- ❑ The goal of treatment being a normal TSH, ideally in the **lower half of the reference range**
- ❑ **L-T3 alone**(standard L-T3 or) sustained release L-T3 is **not recommended** for hypothyroidism treatment
- ❑ **Combination T4 and T3 therapy** has no significant advantage, may be useful in a subgroup of patients who remain symptomatic despite of normal TSH



Thyroid

