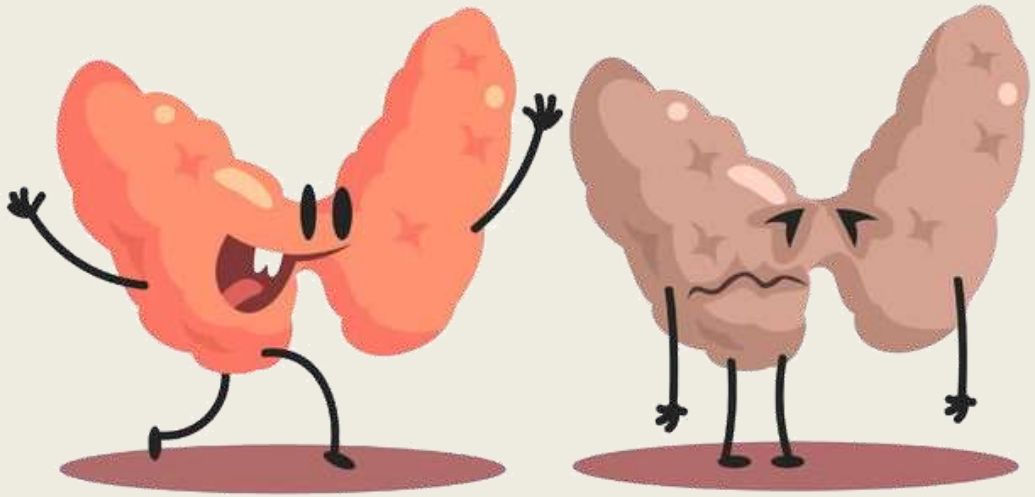
Use of Thyroid Function Tests in Adult, Non-pregnant Patients

EPOMEDICINE



Hypothyroidism

Table 2: Manifestations of Hypothyroidism[4]

Symptoms	Signs
Fatigue, weakness	Slow movement, slow speech
Cold intolerance	Delayed relaxation of tendon reflexes
Dyspnea on exertion	Bradycardia
Weight gain	Carotenemia
Depression, cognitive dysfunction	Coarse skin
Edema	Puffy facies, loss of eyebrows
Constipation	Periorbital edema
Growth failure	Enlargement of the tongue
Hoarseness, Dry skin	Diastolic hypertension
Menorrhagia	Pleural, pericardial effusions
Myalgia and paresthesia	Ascites
Decreased hearing	Galactorrhea
Arthralgia	

Symptoms	(%)
Fatique	88
Cold intolerance	84
Dry skin	77
Voice hoarseness	74
Decreased hearing	40
Sleepiness	68
Impaired memory	66
Weight gain	72
Paresthesia	56
Constipation	52
Hair loss	41

Signs	(%)
Dry coarse skin	90
Voice hoarseness	87
Facial periorbital oedema	76
Slowed movements	73
Mental impairment	54
Bradycardia <60/min	10
Bradycardia>60/min	90

Hyperthyroidism

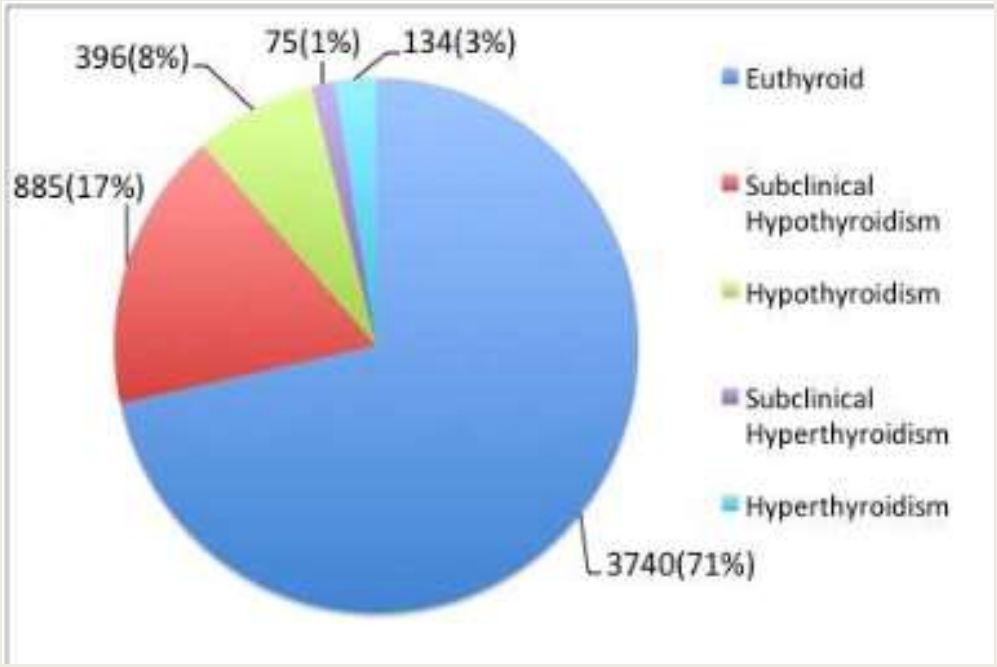
Table 3: Manifestation of Hyperthyroidism
Symptoms
Nervousness , irritability, anxiety, insomnia
Palpitation, tachycardia
Heat intolerance, increased sweating
Thirst, polyuria
Weight loss or gain
Changes in appetite
Oligomenorrhoea, loss of libido, erectile dysfunction
Diarrhoea
Signs
Sinus tachycardia
Fine tremor, hyperkinesia, hyperreflexia
Warm, moist skin
Palmar erythema
Hair loss
Muscle weakness, wasting
Congestive heart failure, chorea, periodic paralysis

Table 1. Clinical Findings in Thyrotoxicosis.

Clinical Manifestations	Percent	Clinical Manifestations	Percent
Tachycardia	100	Weakness	70
Goiter	98	Increased appetite	65
Nervousness	99	Eye complaints	54
Skin changes	97	Leg swelling	35
Tremor	97	Hyperdefacation	33
Sweating	91	Diarrhea	23
Hypersensitivity to heat	89	Atrial fibrillation	10
Palpitations	89	Splenomegaly	10
Fatigue	88	Gynecomastia	10
Weight loss	85	Anorexia	9
Bruit over thyroid	77	Liver palms	8
Dyspnea	75	Constipation	4
Eye Signs	71	Weight Gain	2

Williams RH. *J Clin Endocrinol Metab* 1946:6:1.

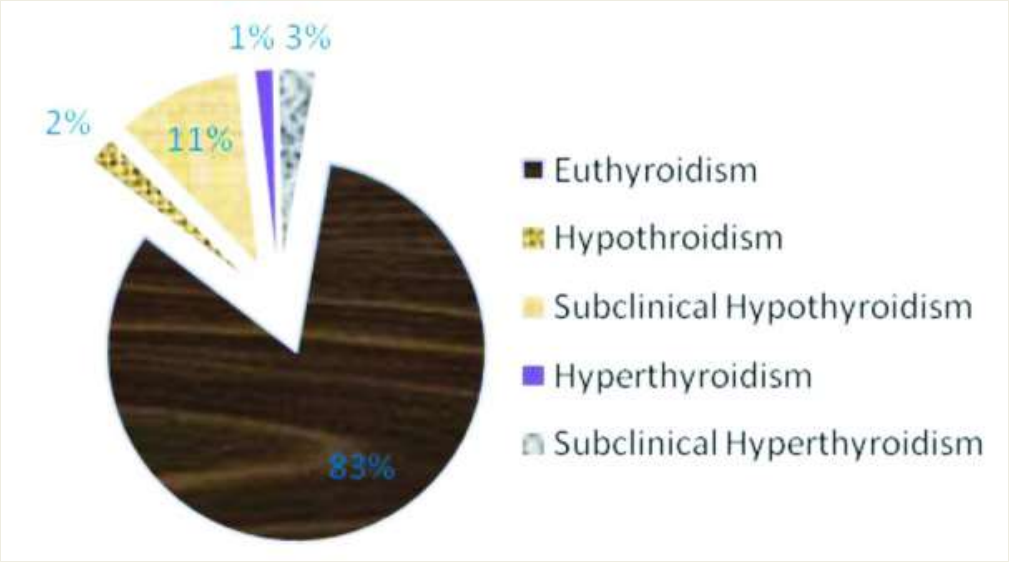
Prevalence of thyroid disorders in Nepal



- **Subclinical hypothyroidism:** 17%
- **Hypothyroidism:** 8%
- **Hyperthyroidism:** 3%
- **Subclinical hyperthyroidism:** 1%

Higher prevalence was seen in age group: ***31-45***
5230 subjects in TUTH

R.V. Mahato et al. (2015) Int J Appl Sci Biotechnol, Vol 3(1): 119-122 DOI: 10.3126/ijasbt.v3i1.12218



- **Subclinical hypothyroidism:** 11%
- **Hypothyroidism:** 2%
- **Hyperthyroidism:** 1%
- **Subclinical hyperthyroidism:** 3%

Higher prevalence was seen in age group: ***41-50***
1504 subjects in Charak Hospital (Pokhara)

Yadav RK, Magar NT, Poudel B, Yadav NK, Yadav B. A prevalence of thyroid disorder in Western part of Nepal. J Clin Diagn Res. 2013 Feb;7(2):193-6. doi: 10.7860/JCDR/2013/4833.2724. Epub 2013 Feb 1. Retraction in: J Clin Diagn Res. 2015 Jul;9(7):ZZ02. PubMed PMID: 23542475; PubMed Central PMCID: PMC3592272.

Thyroid function tests

- TSH
- Free T4 (fT4)
- Free T3 (fT3)

A range of other tests is also available to determine the specific causes of thyroid disease.

Which TFT?

- Strategy of 1st line TSH - may be cost-effective
- When measurement of both TSH and fT4 is required?
  - Optimizing LT4 therapy in newly diagnosed hypothyroidism
  - Monitoring thyroid disorders in pregnancy
  - Monitoring hyperthyroid patients in early months after treatment
  - Diagnosing and monitoring treatment of central hypothyroidism, thyroid hormone resistance and TSH secreting pituitary adenomas
  - Women with type I Diabetes
- fT3 is rarely indicated
  - Reserved for situations where thyroid disease is suspected clinically and TSH is abnormal but fT4 is inappropriately normal

When to test?

- Features of thyroid disorders
- Screening for congenital hypothyroidism
- Suspected goitre
- Atrial fibrillation, hyperlipidemia, osteoporosis, subfertility
- Women with type 1 Diabetes
- Non-specific signs and symptoms in patients who have risk of thyroid disease

Risk factors for thyroid disease

- Men ≥ **60 years age** and Women ≥ **50 years age**
- **Personal or family history** of thyroid disease
- Other **autoimmune diseases**
- Past history of **neck irradiation, thyroidectomy or RAI ablation**
- **Lithium or amiodarone** therapy
- Dietary factors (**Iodine** deficiency or excess)
- Certain chromosomal or genetic disorders (**Turner's, Down's** and Mitochondrial diseases)

Surveillance of "At risk" patients

- **Annual check:**
  - Patients stabilized on LT4
  - Type 1 Diabetes
  - Type 2 Diabetes – only if TSH >2mU/L and TPO Ab +ve
  - Treated hyperthyroidism
  - Down's and Turner's syndrome
  - Post-neck irradiation
  - Untreated subclinical hypothyroidism with TPO Ab +ve
  - Past history of post-partum thyroiditis
- **Lithium or Amiodarone:** 6 monthly check
- **RAI or thyroidectomy:** 4-8 weeks post-treatment → 3 monthly upto 1 year →annually
- **Untreated subclinical hypothyroidism, TPO Ab –ve:** 3 yearly

Hypothyroidism – Diagnosis and When to treat?

1. **TSH > 10mU/L and fT4 below reference range:** Overt primary hypothyroidism

2. **TSH above reference range and fT4 within reference range:** Subclinical hypothyroidism (mild thyroid failure)

3. **TSH (↓ or = or mildly ↑) with low thyroid hormones:** Secondary hypothyroidism

Overt primary hypothyroidism: Commence patient on LT4

Subclinical hypothyroidism: Repeat TSH/fT4 at 3 months to exclude transient TSH rise –

1. If TSH >10 mU/L – start on LT4
2. If TSH ≤10 mU/L but above reference upper limit – t/t can be considered if:
    1. Elevated TPO-Ab
    2. Pregnancy or planning pregnancy
    3. Goiter
    4. Dyslipidemia
    5. Established CVS disease or risk factors of CVS disease
    6. Symptoms suggestive of hypothyroidism

T4 replacement

Aim:

1. Make the patient feel well
2. Serum TSH within normal range
3. fT4 within/slightly above reference range

Monitoring:

T4 dose change →Retest TSH + fT4 after 2-3 months → Stabilized on T4 → Annual TSH

<u>Secondary hypothyroidism:</u> fT4 (TSH is often low)

Strategy:

1. **Starting dose:** 50- 100µg (1.6µg/kg on average)
2. **Alteration of the dose:** using 25-50µg increments and repeat TSH 2-3 months after a change in dose.
3. **Elderly patients and patients with IHD; Subclinical hypothyroidism:** Commence replacement with 25-50µg and increase dose with 12.5-25µg

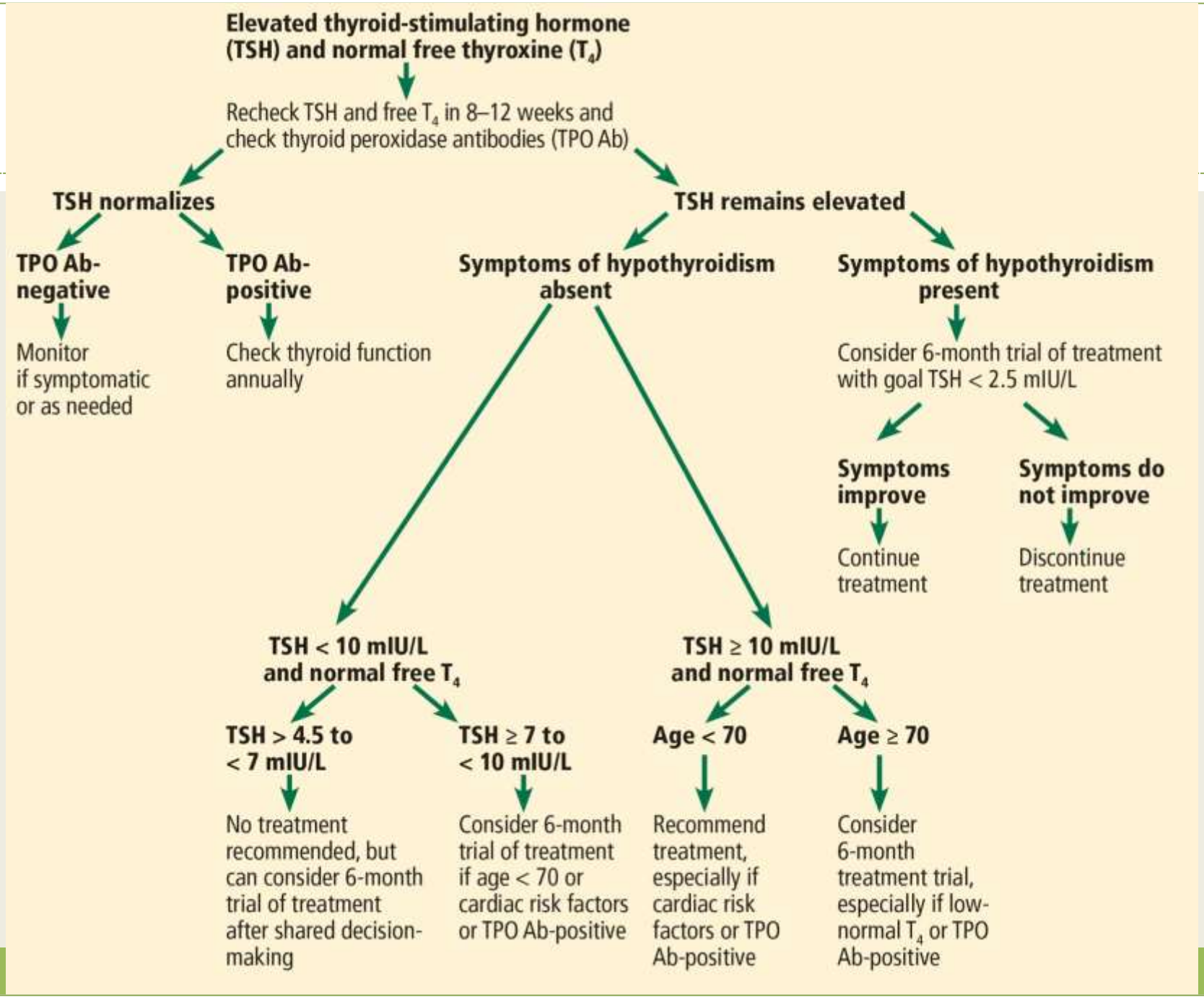
If TSH is below reference range:

1. Reduction in T4 dose is recommended to bring TSH within normal range
2. TSH suppression may result in cardiac problems or bone loss

Optimal dose for long-term therapy: Assessed by TFT with clinical findings

Drugs and T4 therapy

- Some OTC medications can impair T4 absorption – **PPIs, H2 antagonists**, calcium carbonate, soy protein, aluminium hydroxide, ferrous sulphate
- Do not take T4 within **4 hours** of taking other medications
- Requirement for T4 is likely to increase during: **pregnancy**, commencement of **anti-convulsants** or **OCPs**


Elevated thyroid-stimulating hormone (TSH) and normal free thyroxine (T_4)
Recheck TSH and free T_4 in 8–12 weeks and check thyroid peroxidase antibodies (TPO Ab)
TSH normalizes
TSH remains elevated
TPO Ab-negative
TPO Ab-positive
Symptoms of hypothyroidism absent
Symptoms of hypothyroidism present
Monitor if symptomatic or as needed
Check thyroid function annually
Consider 6-month trial of treatment with goal TSH < 2.5 mIU/L
Symptoms improve
Symptoms do not improve
Continue treatment
Discontinue treatment
TSH < 10 mIU/L and normal free T_4
TSH ≥ 10 mIU/L and normal free T_4
TSH > 4.5 to < 7 mIU/L
TSH ≥ 7 to < 10 mIU/L
Age < 70
Age ≥ 70
No treatment recommended, but can consider 6-month trial of treatment after shared decision-making
Consider 6-month trial of treatment if age < 70 or cardiac risk factors or TPO Ab-positive
Recommend treatment, especially if cardiac risk factors or TPO Ab-positive
Consider 6-month treatment trial, especially if low-normal T_4 or TPO Ab-positive

Secondary hypothyroidism

- **Establish extent of hypopituitarism** – measure sex steroids

- **If cortisol deficiency:** Treatment with appropriate glucocorticoid should be initiated before T4 therapy (prevent Addisonian crisis)

- **T4 therapy:**

- Increasing 25 mcg doses
- Target: fT4 within upper 3rd of reference range
- Assess response: fT4; Annual check

Table 4. Elements of Follow-up for Hypothyroidism

Category	*Issue*	*How?*	*How often?*	*Note*
History	Weakness	Question	Every visit	Improvement expected
History	Lethargy	Question	Every visit	Improvement expected
History	Fatigue	Question	Every visit	Improvement expected
History	Cold intolerance	Question	Every visit	Improvement expected
History	Impaired memory	Question	Every visit	Improvement expected
History	Adherence	Question	Every visit	Adherence essential
History	Other drugs	Question	Every visit	May interfere with LT_4
Physical examination	Dry skin	Palpation	Every visit	Improvement expected
Physical examination	Coarse skin	Palpation	Every visit	Improvement expected
Physical examination	Periorbital puffiness	Inspection	Every visit	Improvement expected
Laboratory	TSH	Measure by second-generation TSH assay	q6–8 wk until normal, 3–6 mo later, then annually	Normal: 0.5–5.0 mU/L; Optimal: 0.5–2.0 mU/L

LT_4 = levothyroxine; TSH = thyroid-stimulating hormone.

Hyperthyroidism – Diagnosis and when to treat?

- **TSH <0.01 mU/L and high fT4 and/or T3:** Overt primary hyperthyroidism

- **TSH <0.01 mU/L and normal fT4/T3:** Subclinical hyperthyroidism

- Clinical picture:
  - Ophthalmopathy, Diffuse goiter in Grave's disease
  - Nodular goiter in toxic nodular hyperthyroidism
  - Thyroid pain/tenderness, often with history suggestive of viral illness: Subacute thyroiditis

- If such clinical signs absent:
  - TPO Ab +ve, TSH-R Ab +ve: Suggest Grave's disease
  - RAI scanning:
    - Diffuse uptake: Grave's disease
    - 1 or more hot nodules: toxic nodular hyperthyroidism
    - Reduced or absent uptake: All types of thyroiditis

- **Normal fT4 with subnormal TSH:** measure fT3 (to identify T3 thyrotoxicosis)
- **Important to identify cases of thyroiditis** - standard treatment with thionamides/RAI is ineffective and contraindicated
- **Amiodarone associated hyperthyroidism diagnosed only if:** high fT4 with high/normal fT3 with undetectable TSH

- **Most patients require definitive treatment:** 131 Iodine
- **Mild clinical/biochemical disease:** Prompt treatment with 131 Iodine (without preceding thionamide)
- **Severe clinical/biochemical disease:** Thionamides for 2-3 months until fT4 is normal or near-normal

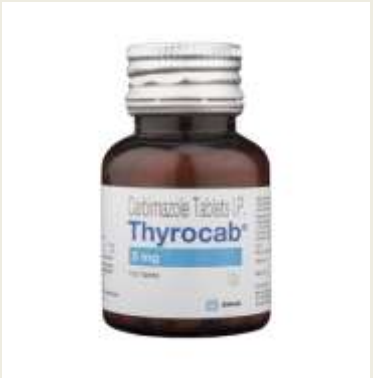
- **Short term thionamide (Carbimazole or PTU):** Preparation for definitive treatment with RAI or surgery
- **Medium term thionamide:** In hope of inducing remission in Grave's disease
- **Long term thionamide:** If definitive treatment is relatively contraindicated (e.g. elderly frail subjects with limited life expectancy)

- **Marked adrenergic symptoms:** Beta-blockers for rapid relief of symptoms
- **Thyroiditis:** Beta-blockers are usually sole form of treatment
  - Severe persistent symptoms/signs in subacute thyroiditis: may require additional therapy with salicylates and/or glucocorticoids
- All patients proceeding to surgery should be rendered euthyroid with thionamides

Thionamide therapy

Monitorning:

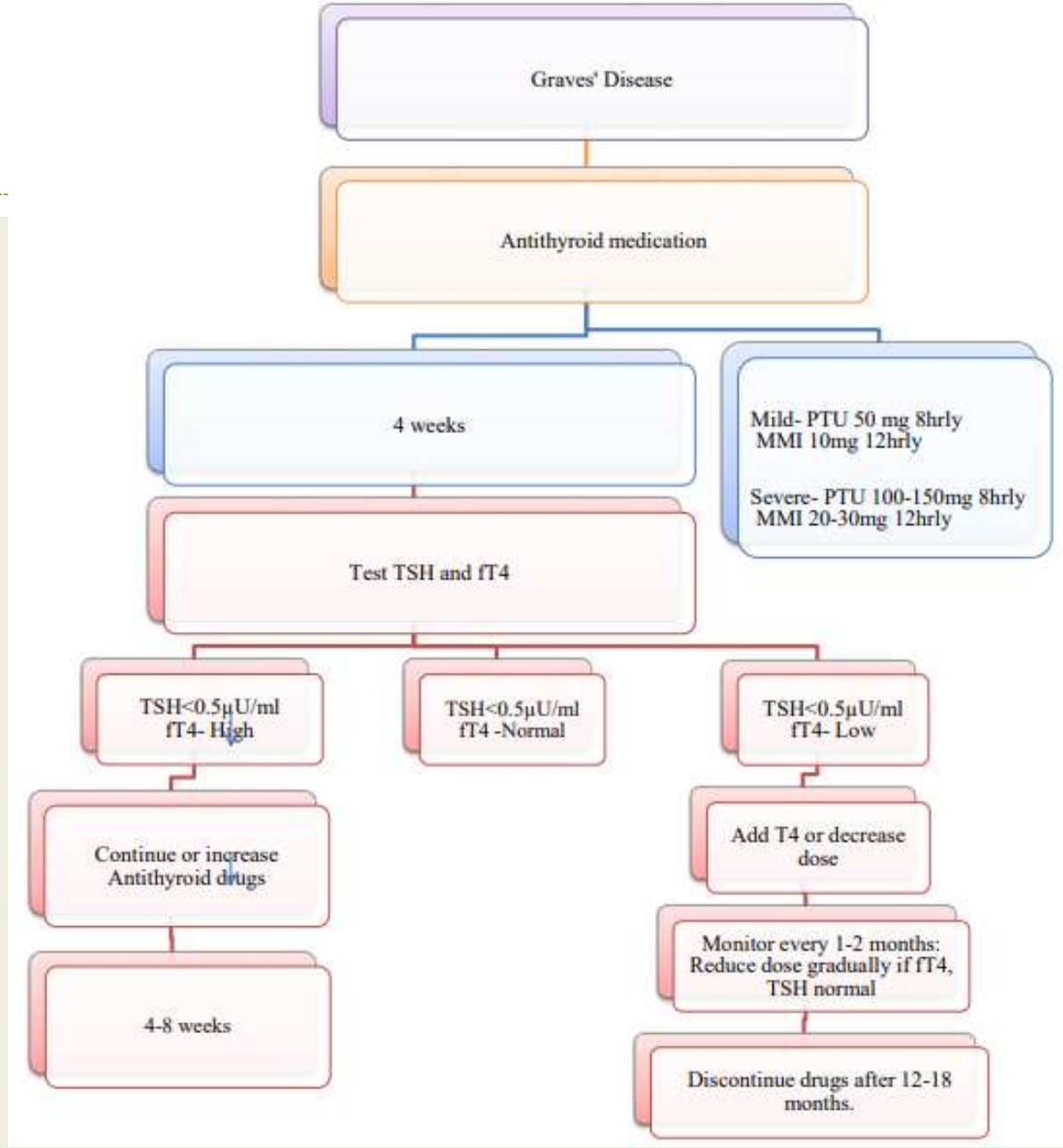
- fT4 and TSH



- Marker of choice to guide therapy:
  fT4 (fT3 in cases of T3 thyrotoxicosis)

- Thionamide started → TFT every 4-6 weeks →
  Maintenance dose achieved → TFT every ~3months

- Dose reduction:
  - Fall in fT4 to low normal or below normal range
  - Rise in serum TSH


Graves' Disease
Antithyroid medication
4 weeks
Mild- PTU 50 mg 8hrly
MMI 10mg 12hrly
Severe- PTU 100-150mg 8hrly
MMI 20-30mg 12hrly
Test TSH and fT4
TSH<0.5µU/ml
fT4- High
TSH<0.5µU/ml
fT4 -Normal
TSH<0.5µU/ml
fT4- Low
Continue or increase
Antithyroid drugs
Add T4 or decrease
dose
Monitor every 1-2 months:
Reduce dose gradually if fT4,
TSH normal
4-8 weeks
Discontinue drugs after 12-18
months.

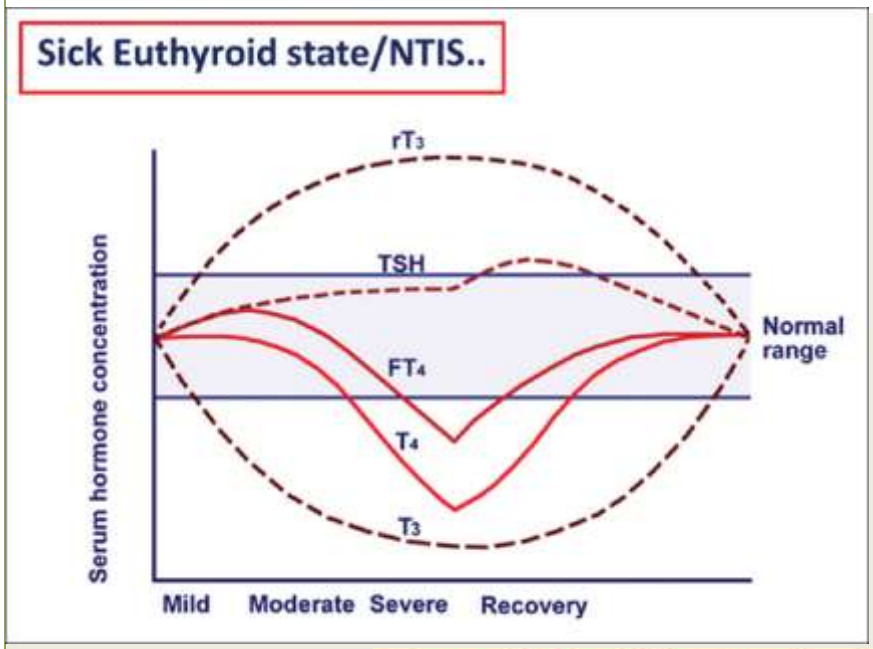
RAI Therapy

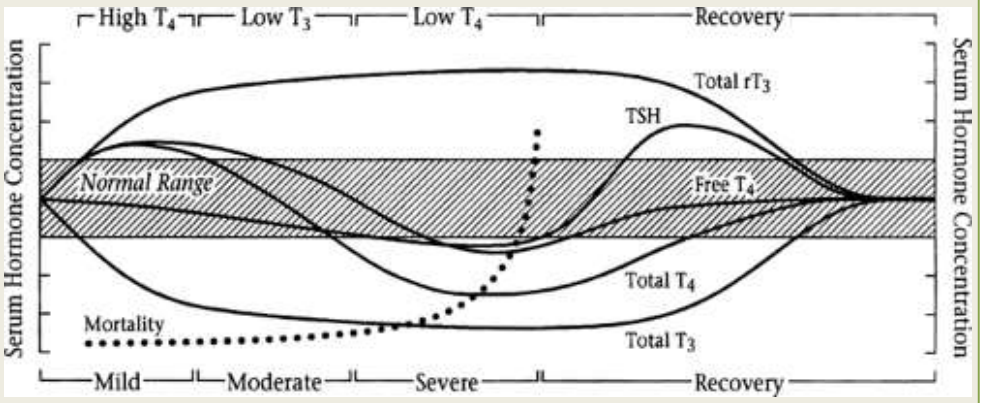
- TFT every 4-6 weeks for at least six months → fT4 remains within reference range → Annual TFT
- **Dose reduction or withdrawal of thionamide:** A fall in FT4 to below the reference range or a rise in TSH to above the reference range
- **TSH >20mU/L** following RAI therapy in a patient not receiving thionamides in the previous 4-6 weeks should trigger **LT4 therapy**

Subclinical hyperthyroidism

- Exclude moderate and severe illness (non-thyroidal illness) and drugs that suppress TSH (dopaminergic drugs, high dose glucocorticoids)
- Repeat TSH/fT4/T3 1-2 months later
- If abnormalities persist – Refer to endocrinologist
- If treatment is not undertaken – monitor TFT every 6-12 months

Non-thyroidal illness/Sick euthyroid syndrome/ Low T3 syndrome

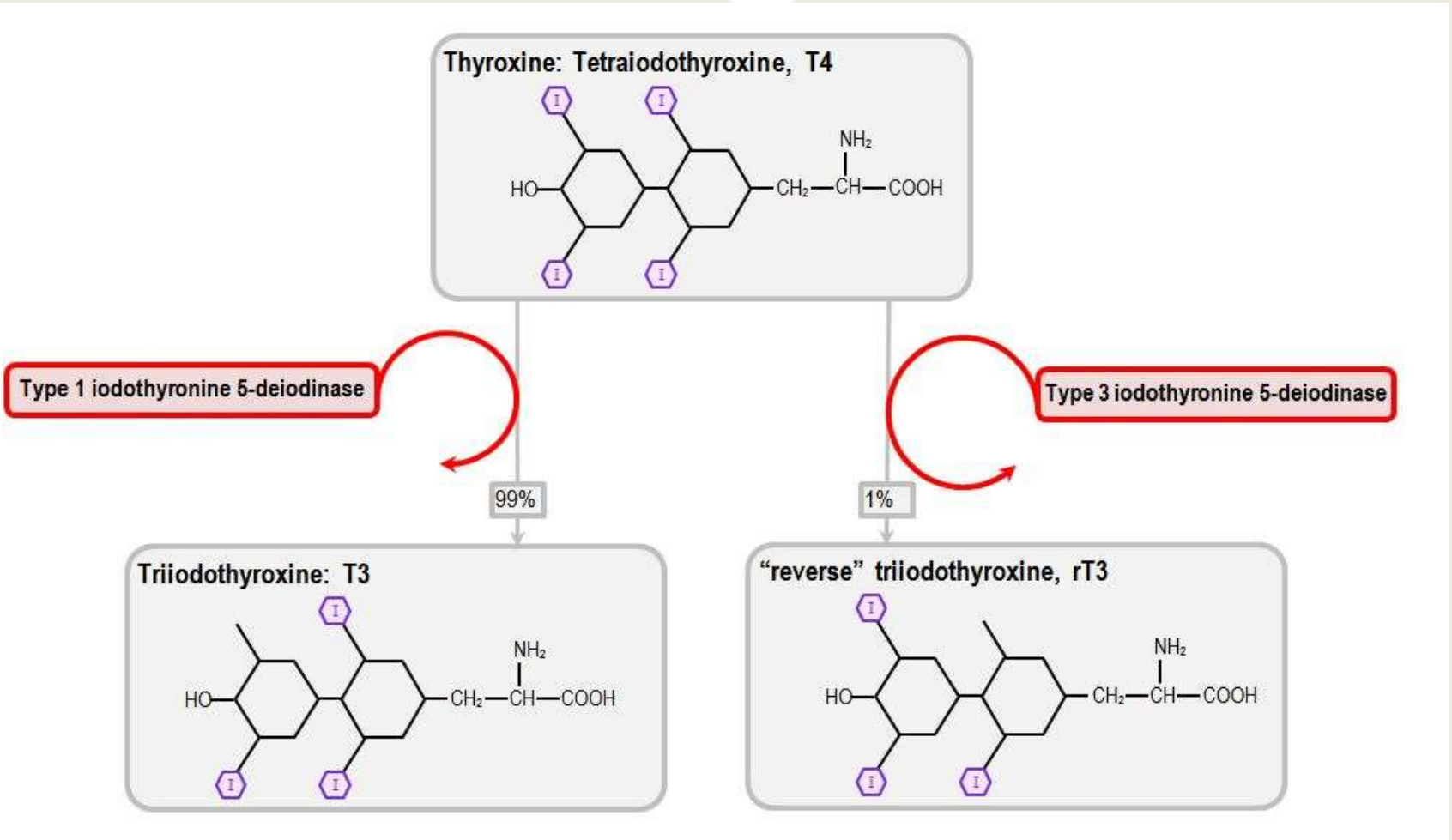




Changes in thyroid hormone levels during illness

Severity of illness	TSH	Total T_3	Free T_4	Reverse T_3	Probable cause
Mild	No change	Mildly decreased	No change	Mildly increased	Mildly decreased D2, D1
Moderate	No change or mildly decreased	Decreased	No change or mild increase or decrease	Increased	Decreased D2, D1, possibly mildly increased D3
Severe	Decreased	Markedly decreased	Mildly decreased	Mildly increased	Decreased D2, D1, possibly mildly increased D3
Recovery	Mildly increased	Mildly decreased	Mildly decreased	Mildly increased	Unknown

D1 through D3 = iodothyronine deiodinases; T_3, triiodothyronine; T_4 = thyroxine; TSH = thyroid-stimulating hormone (thyrotropin).


Thyroxine: Tetraiodothyroxine, T4
HO
NH2
CH2—CH—COOH
Type 1 iodothyronine 5-deiodinase
Type 3 iodothyronine 5-deiodinase
99%
1%
Triiodothyroxine: T3
"reverse" triiodothyroxine, rT3

TFT in Hospitalized patients

- **TSH <0.1 mU/L:** non-thyroidal illness (≥2x) vs hyperthyroidism
- **Increased TSH:** recovery from illness = hypothyroidism
- **TFT only if:** clinical suspicion of thyroid problem
- **Non-thyroid illness vs thyroid disorder:**
  - fT3 (decreased)
  - Repeat test (transient)
- **If TSH >20 mU/ml or undetectable:** euthyroid sick syndrome less likely

TPO Antibody

Clinical use:

- Diagnosis of autoimmune thyroid disorder
- As a risk factor for autoimmune thyroid disorder
- As a risk factor for hypothyroidism during treatment with IFN-alpha, IL-2 or lithium
- As a risk factor for thyroid dysfunction during lithium or amiodarone therapy

Measure TPO Ab on one occasion for diagnosis of autoimmune thyroiditis, but **not for monitoring**

Thyroglobulin antibody

- No additional value over TPO-Ab; no need if TPO-Ab is present
- Only role:
  - In differentiated thyroid cancer – to determine possible interference with Tg measurement
  - Prognostic indicator – serial measurements
- Tg and Tg-Ab should be measured in same specimen

TSH Receptor Antibody

- Particularly useful in pregnancy

- May also be useful:
  - To investigate hyperthyroidism of uncertain etiology
  - To investigate patient with suspected “euthyroid Graves’ ophthalmopathy
  - For pregnant women with past and present history of Graves’ disease
  - To identify neonates with transient hypothyroidism due to TSH blocking antibodies

References

- UK guidelines for the use of Thyroid function tests – British thyroid association (July, 2006)
- A Quick Reference Guide for Use of Thyroid Function Tests in Primary Care – Dr. Gerard Boran, Dr. Niamh Moran, Dr. Anne McGowan, Dr. Mark Sherlock, Dr. James Gibney
- In the clinic. Hypothyroidism – Michael T Mcdermott (Annals of Internal medicine, 2009)
- Thyroid Function Testing in the Diagnosis and Monitoring of Thyroid Function Disorder – Bcguidelines.ca (2018)

MCQs

1. Patients with subclinical hypothyroidism should be considered for LT4 therapy if the patient has:

A. A family history of thyroid disease

✓ Elevated LDL cholesterol

C. Positive TSHR-AbS antibody

D. A history of hypertension

E. All of the above

2. What is the starting daily dose of LT4 in an 87 kg, 5'4" 32-year otherwise healthy old patient, with overt hypothyroidism?

A. 25 mcg

B. 50 mcg

C. 75 mcg


100 mcg

E. 150 mcg

3. In a patient receiving stable LT4 therapy, laboratory monitoring should be performed every _____.

A. Month

B. 6 to 8 weeks

C. 3 months

 Year

E. 5 years

4. What is the target TSH range (mIU/L or µIU/mL) for patients being treated for hypothyroidism or hyperthyroidism?

A. Undetectable

B. 2.5 to 4.5

C. 1.4 to 2.5


0.5 to 4

E. 4 to 5

THANK YOU