THYROID FUNCTION

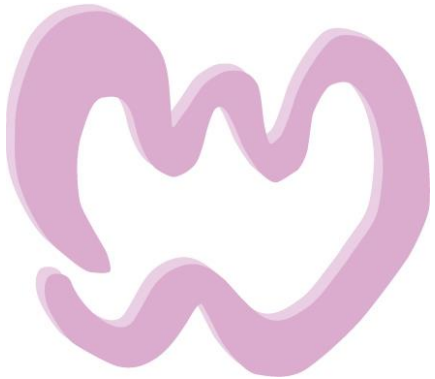
The Thyroid: Driving Metabolism

The thyroid gland produces, stores and secretes thyroid hormones which affect

- Growth and development
- Energy metabolism and oxygen consumption
- Protein and carbohydrate metabolism
- Lipid metabolism
- Bone metabolism
- Cardiovascular system
- Muscle function
- Brain, nervous system, psyche
- Fertility and pregnancy

Aspects of Thyroid Disease

Size
(normal, small, enlarged = goiter)



Function
(normal, hypothyroid, hyperthyroid)

Pathogenesis
(autoimmune, congenital, iodine deficiency, malignancy)

Structure/Morphology
(homogenous, poor in echo, nodules, cysts)

Diagnostics of Thyroid Disorders

Basic examination

- Patient history
- Physical examination
- Palpation of the thyroid gland
- Laboratory
  (TSH and thyroid hormones)

Additional diagnostics

- Ultrasound
- Antibodies
- Fine needle aspiration biopsy
- Nuclear scan (=scintigraphy)

Laboratory Values

Hormones

- TSH (Thyroid-stimulating hormone)
  = most important screening parameter
- fT_4 (free T_4)
- fT_3 (free T_3)

Antibodies

- Anti-TPO (Antibody against thyroperoxidase)
- Anti-TSHR (Antibody against TSH receptor)
  positive in Graves' disease

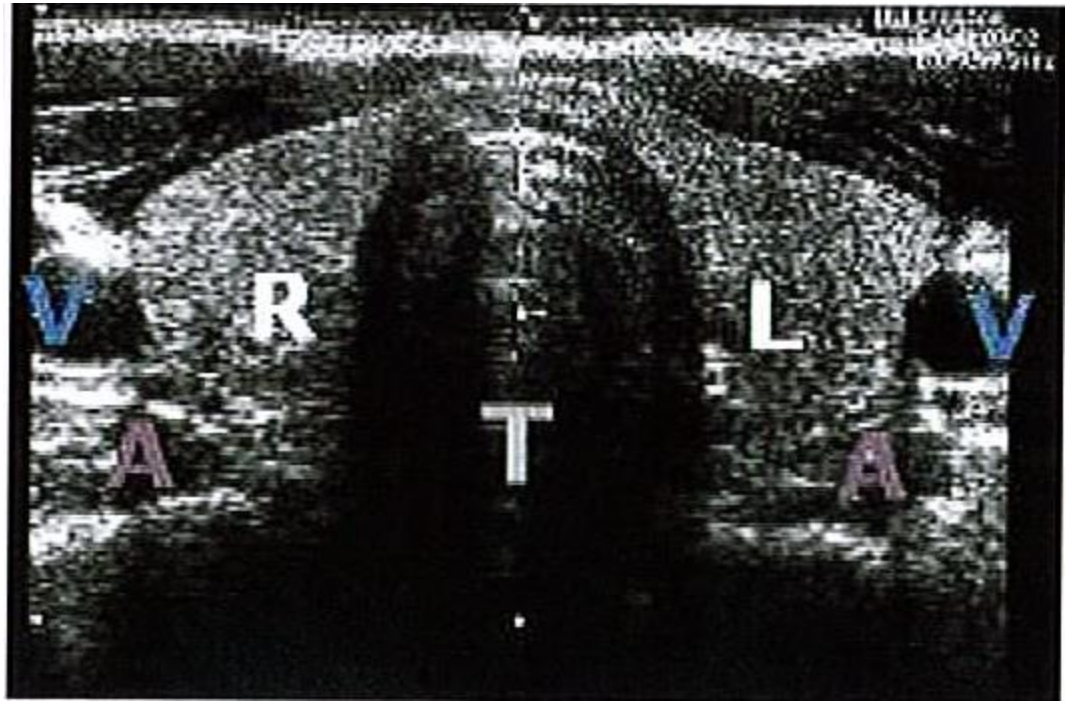
Special diagnostics

- TBG, total hormones TT_4, TT_3
- Tg (thyroglobulin), calcitonin

McPhee and Papadakis 2012 p. 1079
Braverman LE, et al. *The Thyroid*, 9 ed. Philadelphia, PA; Lippincott Williams & Wilkins; 2005

Ultrasound Examination

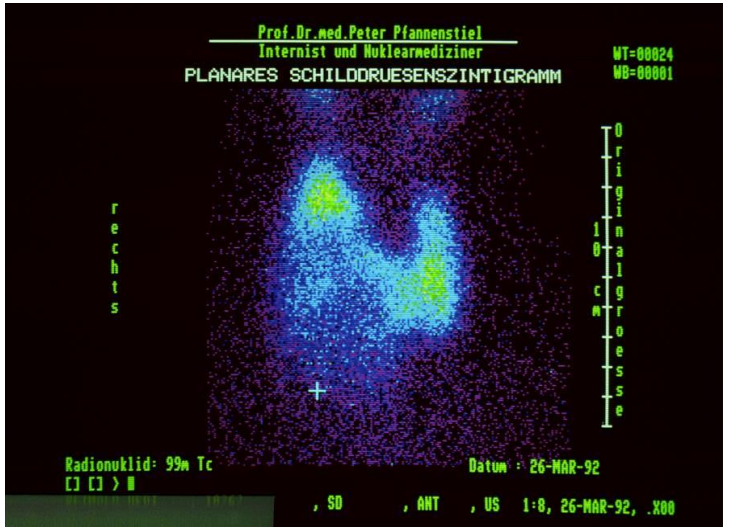
- Measurement of thyroid volume and detection of nodules, cysts and calcifications
- Reference values for thyroid volume:
  women 18 mL, men 25 mL



R = right lobe, L = left lobe,
T = trachea, A = artery, V = vein

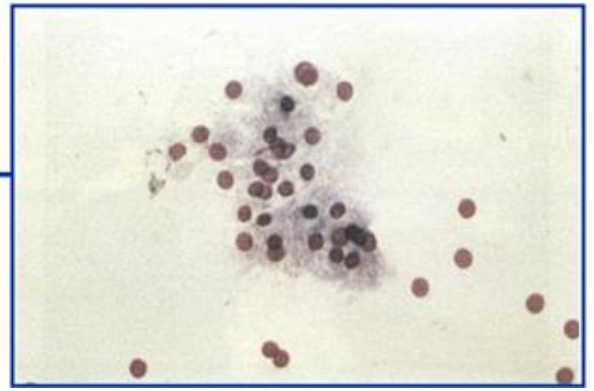
Nuclear Scan (=Scintigraphy)

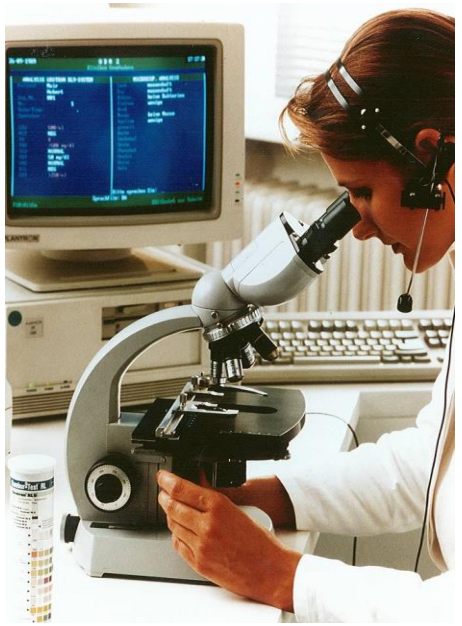
- Injection of radioactive technetium pertechnate (Tc-99m) or radioactive iodine (I-123)
- Scan for over- and underactive (hot/cold) areas
- Indication: nodular goitre



Fine-Needle Aspiration Biopsy (FNAB)

- Puncture of thyroid nodules/cysts and cytological examination
- Check for malignancy (thyroid cancer)





Definitions of Thyroid Function

Euthyroidism

- TSH 0.4–4.0 (2.5) mU/L, fT_4 normal

Mild thyroid failure / subclinical hypothyroidism

- TSH ↑, fT_4 normal

Overt hypothyroidism

- TSH ↑↑, fT_4 ↓

Subclinical hyperthyroidism

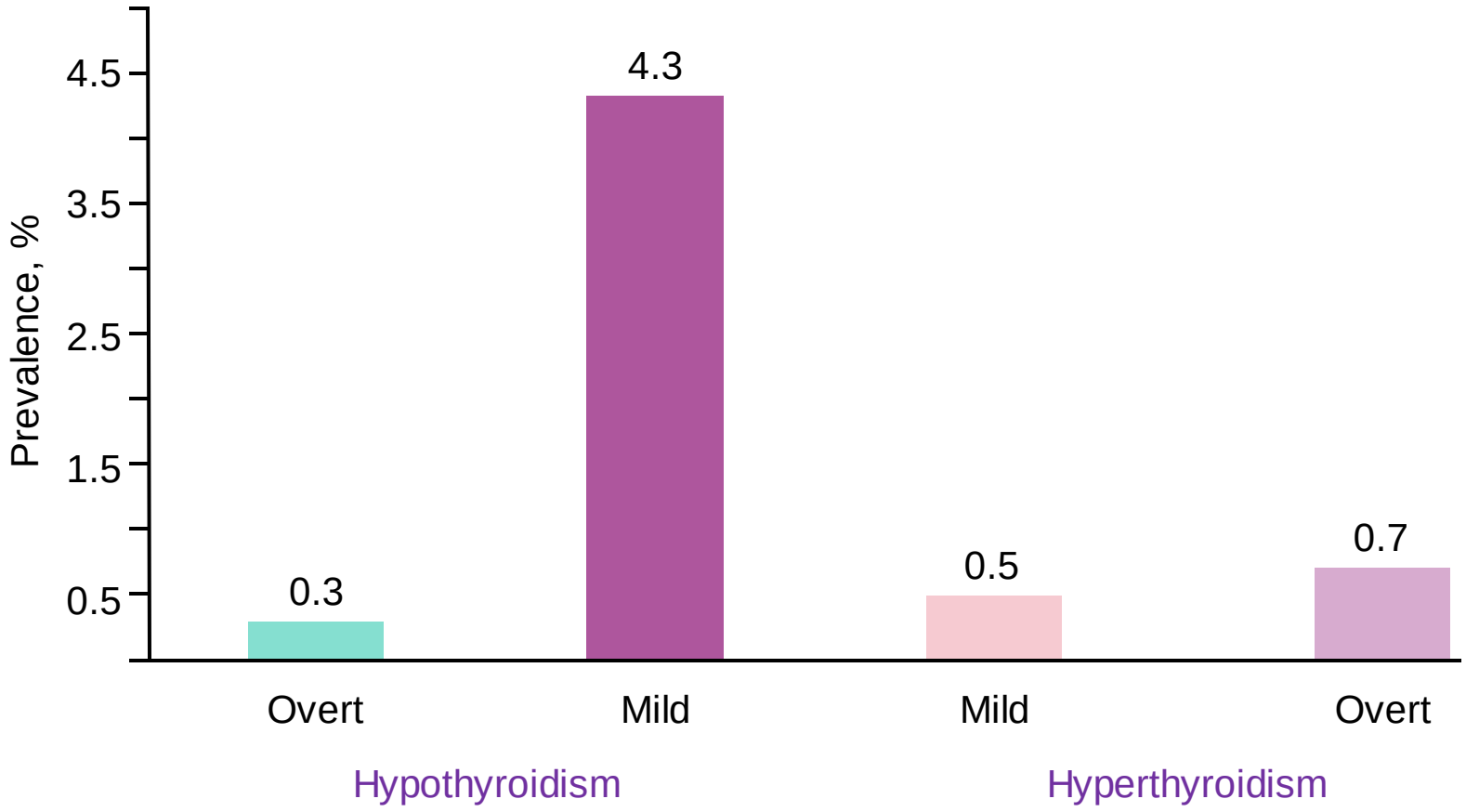
- TSH ↓, fT_4 normal

Overt hyperthyroidism

- TSH ↓↓, fT_3/fT_4 ↑

Garber et al. 2012 p. 1205
Braverman LE, et al. *The Thyroid*, 9 ed. Philadelphia, PA; Lippincott Williams & Wilkins; 2005 p. 697-698

Hypothyroidism and Hyperthyroidism – Prevalences



Data from the National Health and Nutrition Examination Survey (NHANES) III
Hollowell JG, et al. *J Clin Endocrinol Metab* 2002;87:489–499
Kravets American Family Pysiciann 2016;93:363-373

HYPERTHYROIDISM

Definitions of Thyroid Function

Euthyroidism

TSH 0.4–4.0 (2.5) mU/L, fT_4 normal

Subclinical hyperthyroidism

TSH ↓, fT_4 normal

Overt hyperthyroidism

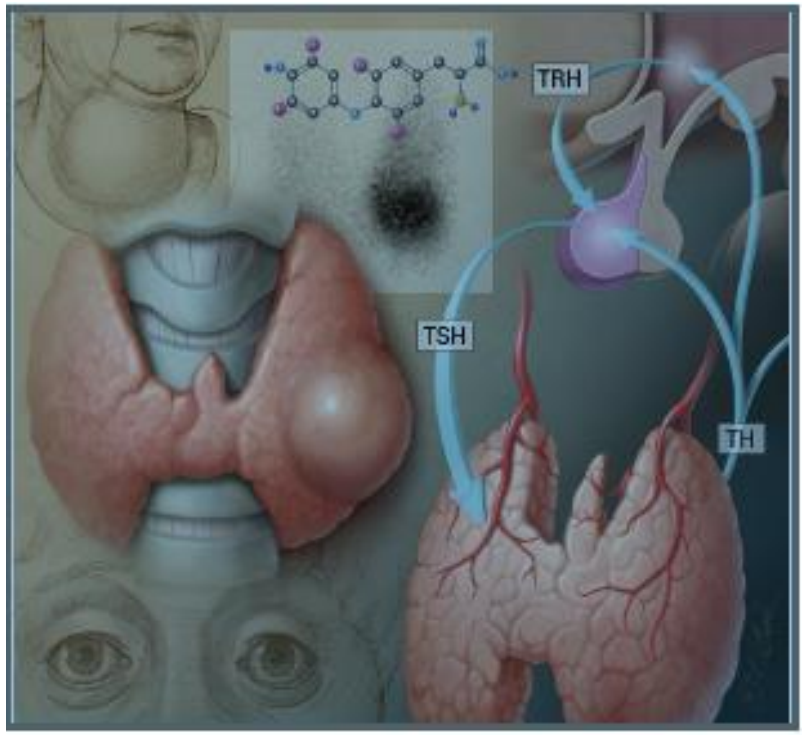
TSH ↓↓, fT_3/fT_4 ↑

Braverman LE, et al. *Werner & Ingbar's The Thyroid. A Fundamental and Clinical Text*, 9th ed. 2005
Vanderpump MP, et al. *Clin Endocrinol (Oxf)* 1995;43:55–68

Hyperthyroidism

Hyperthyroidism refers to excess synthesis and secretion of thyroid hormones by the thyroid gland, which results in accelerated metabolism in peripheral tissues

The prevalence of hyperthyroidism is approximately 0.2-1.3 % (0.5 % overt and 0.7 % subclinical).
2.7% in women
0.23% in men



Hyperthyroidism – Underlying Causes

Hyperthyroidism with a normal or high radioiodine uptake
Autoimmune thyroid disease
Graves' disease
Hashitoxicosis
Autonomous thyroid tissue (uptake may be low if recent iodine load led to iodine-induced hyperthyroidism)
Toxic adenoma
Toxic multinodular goiter
TSH-mediated hyperthyroidism
TSH-producing pituitary adenoma
Non-neoplastic TSH-mediated hyperthyroidism
Human chorionic gonadotropin-mediated hyperthyroidism
Hyperemesis gravidarum
Trophoblastic disease

Hyperthyroidism with a near absent radioiodine uptake
Thyroiditis
Subacute granulomatous (de Quervain's) thyroiditis
Painless thyroiditis (silent thyroiditis, lymphocytic thyroiditis)
Postpartum thyroiditis
Amiodarone (also may cause iodine-induced hyperthyroidism)
Checkpoint inhibitor-induced thyroiditis
Radiation thyroiditis
Palpation thyroiditis

Ectopic hyperthyroidism
Struma ovarii
Metastatic follicular thyroid cancer

Exogenous thyroid hormone intake
Excessive replacement therapy
Intentional suppressive therapy
Factitious hyperthyroidism

Common Signs and Symptoms of Hyperthyroidism

Symptoms

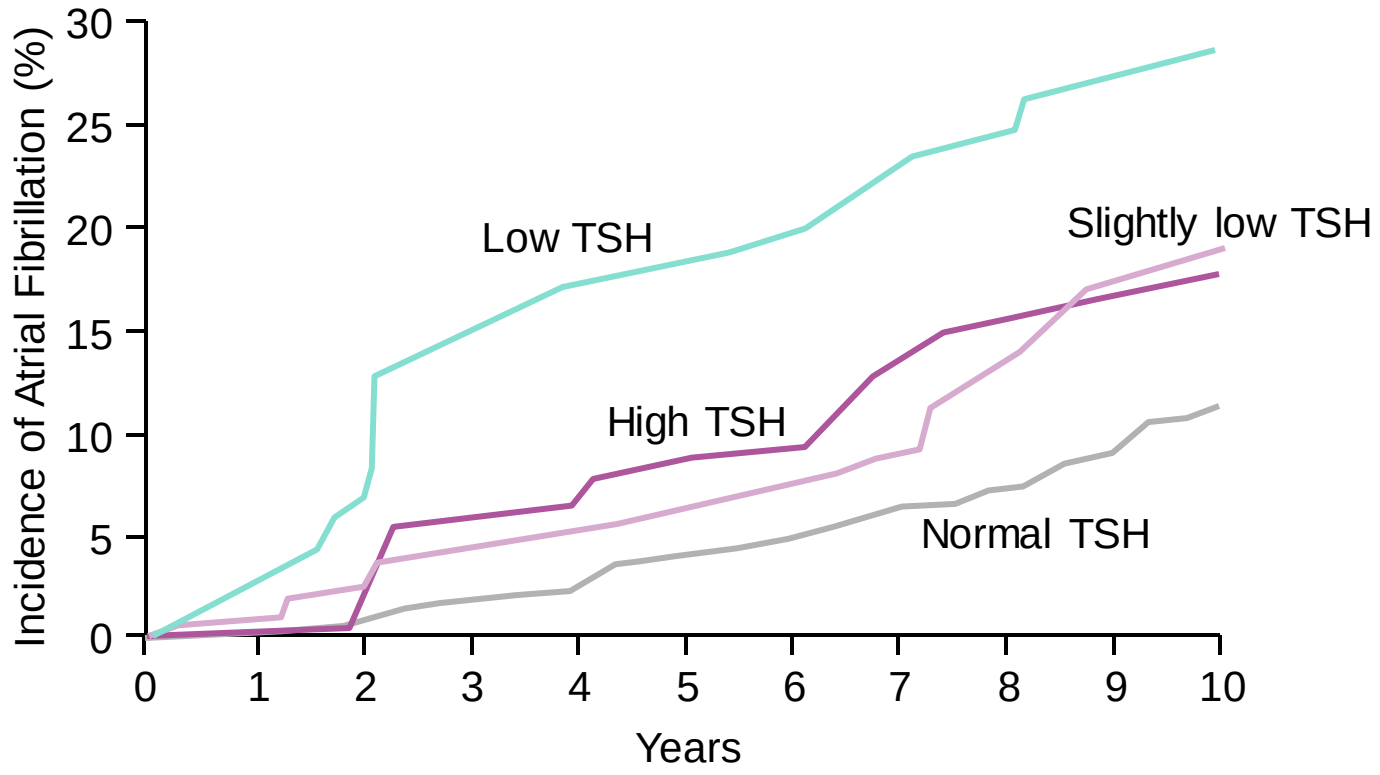
- Nervousness
- Fatigue
- Weakness
- Increased perspiration
- Heat intolerance
- Tremor
- Hyperactivity
- Palpitations
- Increased appetite
- Weight loss
- Menstrual disturbances

Signs

- Hyperactivity
- Tachycardia
- Systolic hypertension
- Warm, moist, or smooth skin
- Stare and eyelid retraction
- Tremor
- Hyper-reflexia
- Muscle weakness
- Goiter

Hyperthyroidism and Atrial Fibrillation

Low TSH and Atrial Fibrillation in Patients >60 Years: Framingham Heart Study



Sawin C, et al. *N Engl J Med* 1994;331:1249; Parle J, et al. *Lancet* 2001;358:861–865

Hyperthyroidism – Diagnostics

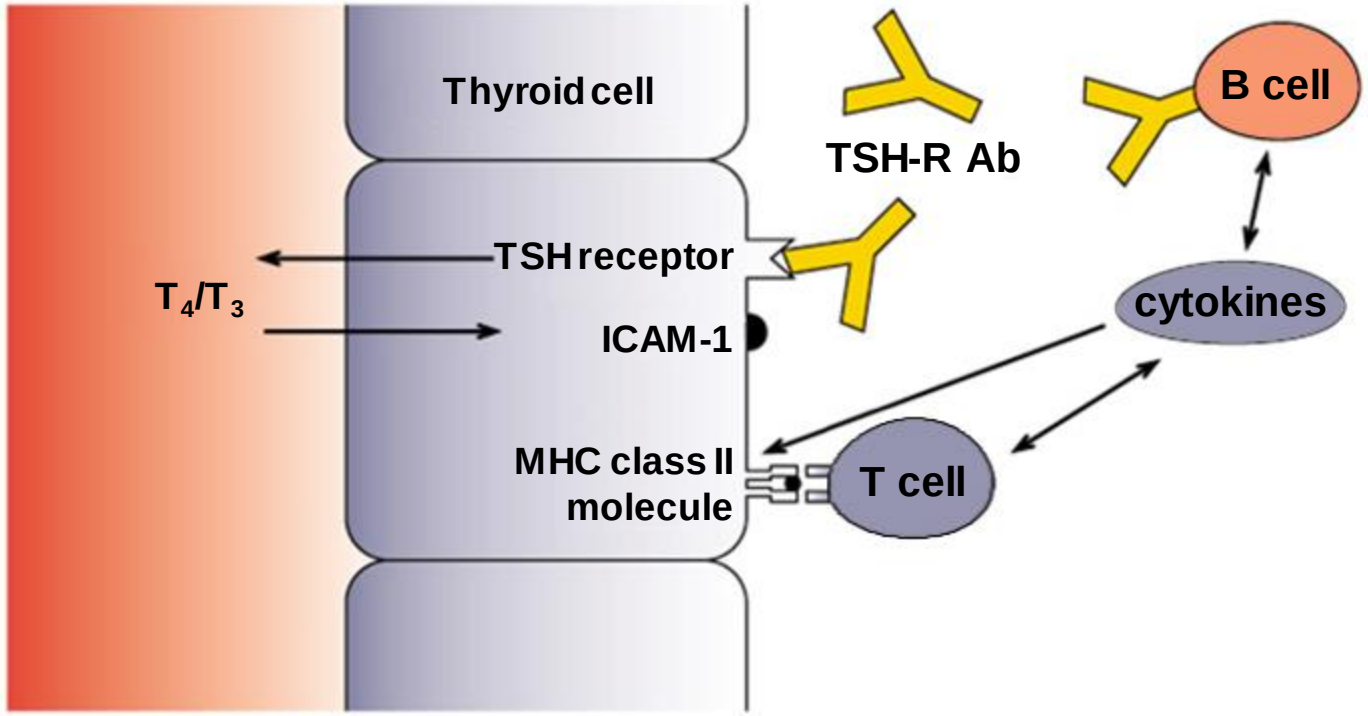
- **Case history (goiter, nodules, autoimmune disease…)**
- **Family history**
- **Clinical examination**
- **Laboratory testing (TSH, fT_4, fT_3, antibodies)**
- **Ultrasonography**
- **Secondary diagnostics:**
  - Aspiration biopsy of nodules
  - Scintigraphy

Graves' Disease (Toxic Diffuse Goiter)

- **The most common cause of hyperthyroidism**
  - Accounts for 60–90% of cases
  - Annual Incidence 20-50 cases per 100 000 persons in general population
  - Affects more females than males, especially in the reproductive age range
- Association with autoimmune pathologies such as thyroiditis, pernicious
- anemia and diabetes mellitus type 1

- Graves' disease is an autoimmune disorder possibly related to a defect in immune tolerance

Graves' Disease – Pathogenesis

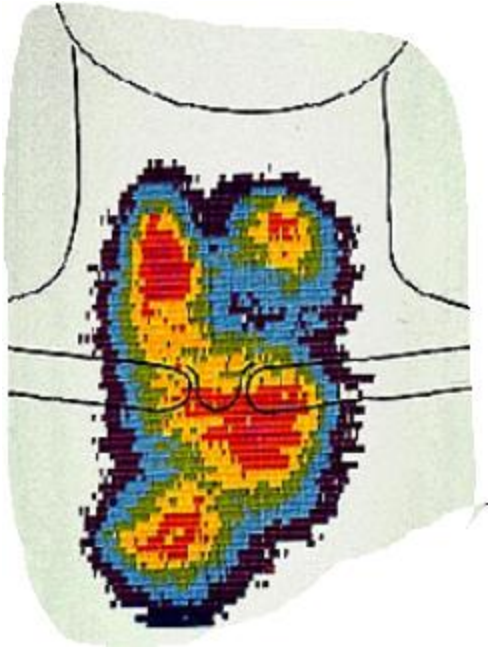


Appearance of TSH receptor auto-antibodies

Hyperthyroidism (Graves' Disease) - Before and After Treatment

Toxic Multinodular Goiter
Toxic Adenoma

- More common in places with lower iodine intake
  - Accounts for less than 5% of thyrotoxicosis cases in iodine-sufficient areas
- Evolution from endemic diffuse goiter to toxic multinodular goiter is gradual
- Thyrotropin receptor mutations and TSH mutations have been found in some patients with toxic multinodular goiters



A

B

Subacute thyroiditis

(subacute granulomatous thyroiditis)

Subacute thyroiditis is presumed to be caused by:

A viral infection or a postviral inflammatory process.

Coxsackievirus, mumps, measles, adenovirus, SARS-CoV-2, and other viral infections

Many patients have a history of an upper respiratory infection prior to the onset of thyroiditis:

(typically two to eight weeks beforehand)

.

The disease was thought to have a seasonal incidence (higher in summer)

Laboratory findings

CBC

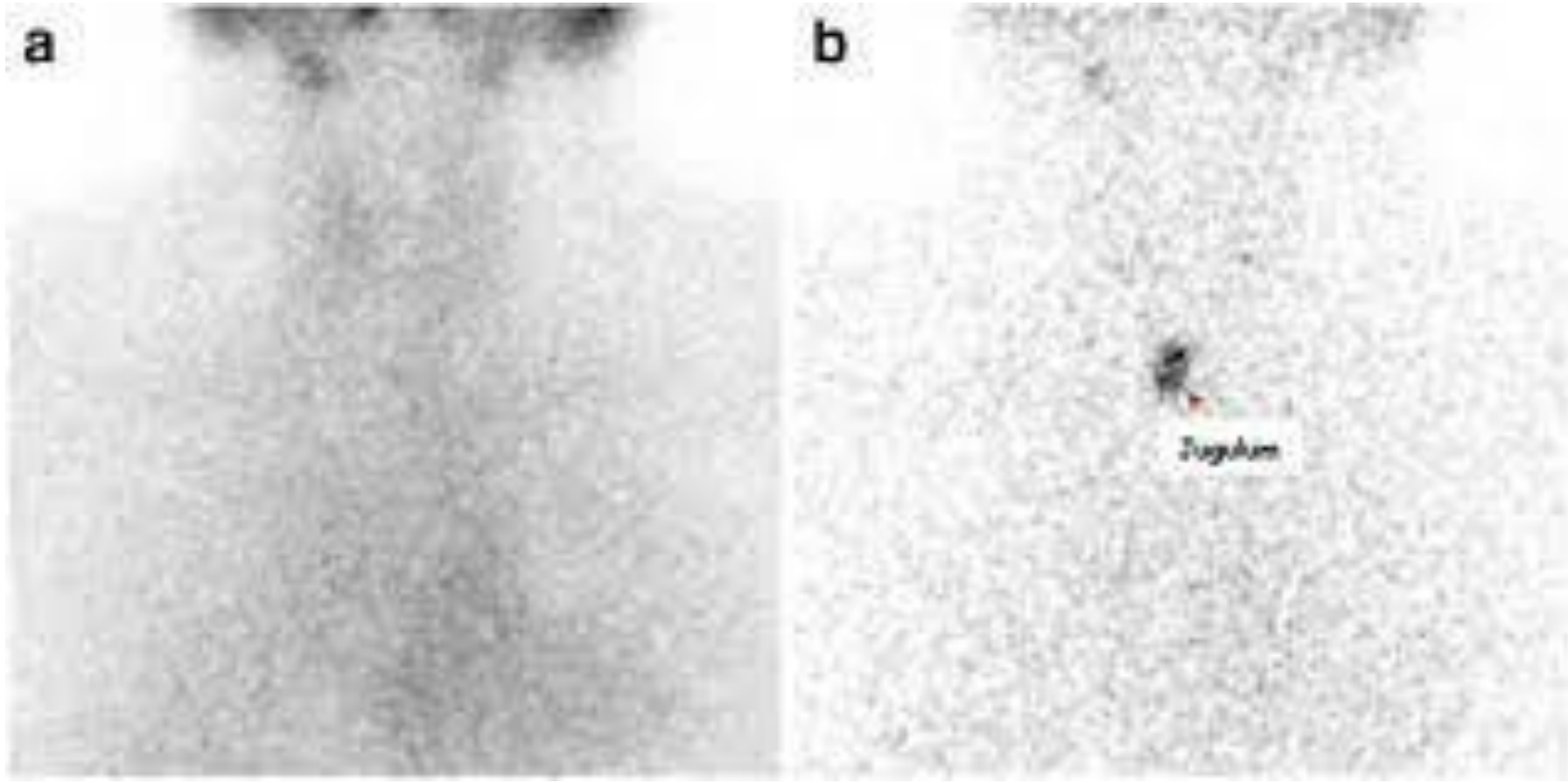
ESR

CRP

FT4 and T3

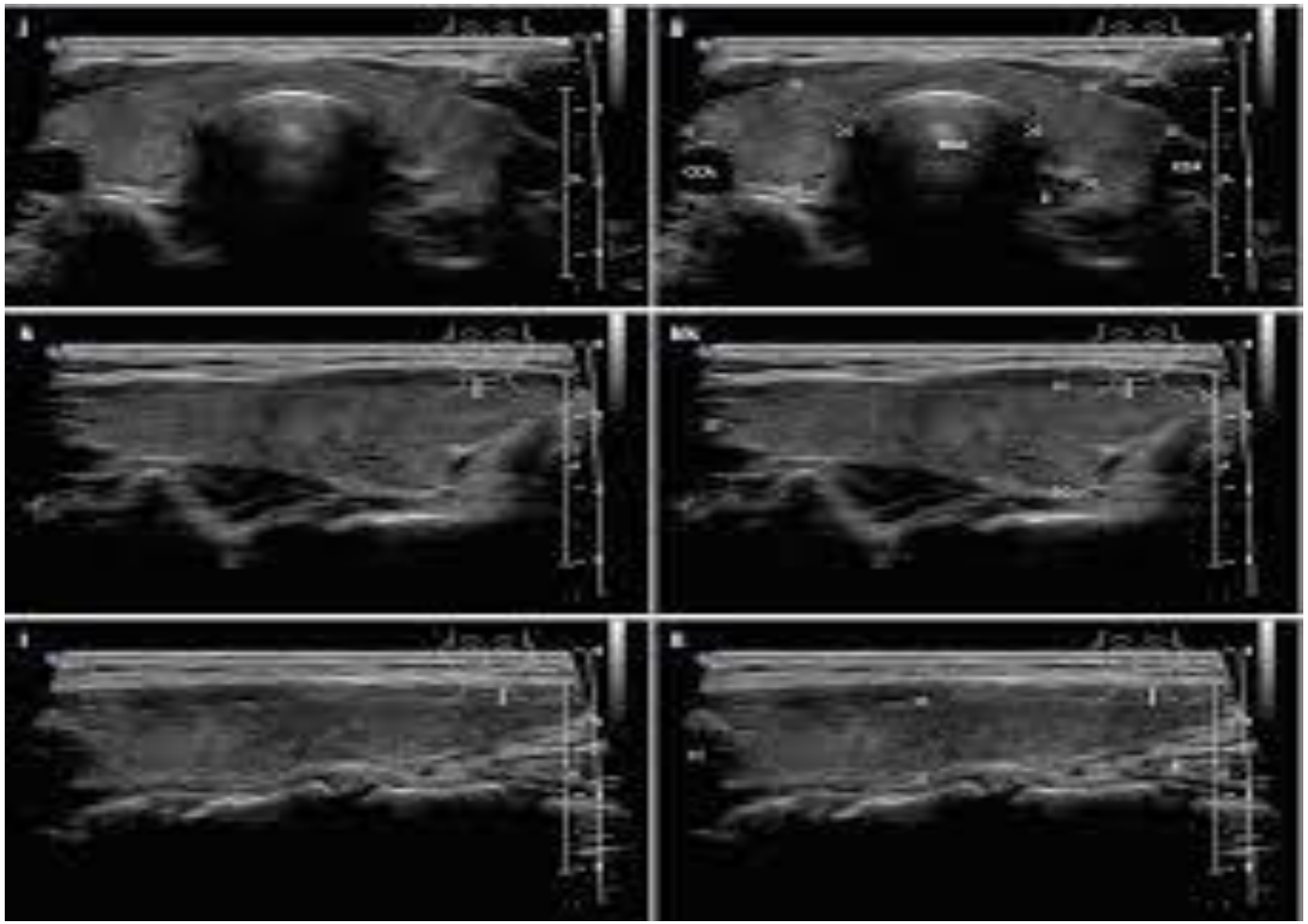
TSH

AST ALT


a
b
Jugulum

ultrasonography

, the thyroid appears to be normal or enlarged but is diffusely or focally hypoechogenic regardless of its size [Color Doppler sonography shows low flow during the hyperthyroid phase,



Hyperthyroidism – Treatment 1/2

Treatment goals

- Eliminate excess of thyroid hormone – re-establishing an euthyriod state
- Relief of symptoms
- Minimize the long-term consequences

Brown 2016
Kahaly et al 2018

Treatment of Graves hyperthyroidism

Therapy	Advantages	Disadvantages
Thionamides	Chance of permanent remission Some patients avoid permanent hypothyroidism Lower initial cost	Minor side effects – Rash, hives, arthralgias, transient granulocytopenia, gastrointestinal symptoms Major side effects – Agranulocytosis, vasculitis (lupus-like syndrome), hepatitis Risk of fetal goiter, hypothyroidism, and birth defects if pregnant Requires more frequent monitoring
Radioiodine	Permanent resolution of hyperthyroidism	Permanent hypothyroidism Patient must take radiation precautions for several days after treatment, avoiding contact with young children and pregnant women Development or worsening of Graves ophthalmopathy Rare radiation thyroiditis Patient concerns about long-term oncogenic effects of radiation
Surgery	Rapid, permanent cure of hyperthyroidism	Permanent hypothyroidism Risks for iatrogenic hypoparathyroidism and recurrent laryngeal nerve damage Risks associated with general anesthesia High cost

Beta blockers ameliorate the symptoms of hyperthyroidism

that are caused by increased beta-adrenergic tone. **These include:**

Palpitations

Tachycardia,

Tremulousnes,

Anxiety,

Heat intolerance.

Iodine solutions, such as saturated solutions of potassium iodide (SSKI) or potassium iodide-iodine (Lugol's solution)

MECHANISM OF ACTION —

Iodine has several effects on thyroid function.
In hyperthyroid patients,

1- iodine acutely inhibits hormonal secretion

2- A second effect involves inhibition of iodine organification in the thyroid gland
thereby diminishing thyroid hormone biosynthesis, a phenomenon called the Wolff-Chaikoff effect

Patients with Graves' hyperthyroidism

- Acutely ameliorates hyperthyroidism by blocking thyroid hormone release
- Inhibits thyroid hormone synthesis

INDICATIONS —

Iodine is primarily used in the short term

- Preoperative preparation for thyroidectomy in Graves' disease
- Adjunctive therapy (one week after radioiodine or with thionamides) in Graves' disease
- Treatment of thyroid storm

Hyperthyroidism – Treatment 2/2

Treatments

Antithyroid drugs – *Decreasing thyroid hormone synthesis*

- ✓ Methimazole
- ✓Carbimazole (prodrug of Methimazole)
- ✓ PTU (Propylthiouracil)

Radioiodine therapy

Surgery

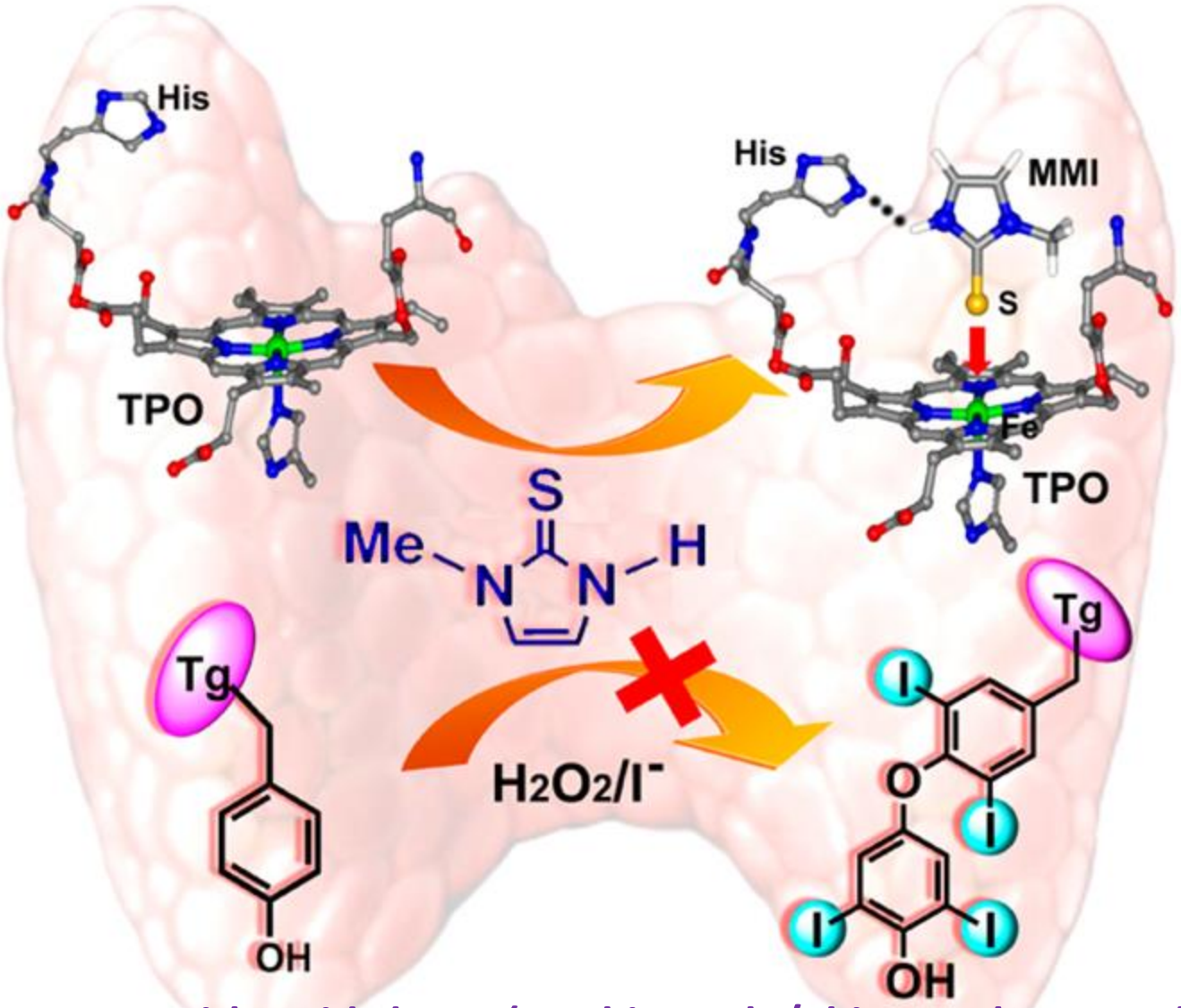
} ***Reducing the amount of thyroid tissue***

Monitoring

TSH, ultrasonography, antibodies

Brown 2016
Kahaly et al 2018

anism of Action



Antithyroid drugs (Methimazole/Thiamazole, Propylthiouracil - PTU) inhibit the thyroid hormone synthesis by blocking the thyroid peroxidase (TPO)-mediated iodination of tyrosine residues in thyroglobulin, a key step in the synthesis of T4

Manna et al. 2013

Hyperthyroidism – Antithyroid drugs

Drug	Initial dose	Maintenance dose	Remark
Methimazole	20–40 mg	2.5–10 mg	First choice
Carbimazole	30–60 mg	5–15 mg	Prodrug of thiamazole
PTU	150–450 mg	50–150 mg	Alternative, in pregnancy

SUBCLICAL HYPERTHYROIDISM

Definitions of Thyroid Function

Euthyroidism

TSH 0.4–4.0 (2.5) mU/L, fT_4 normal

Subclinical hyperthyroidism

TSH ↓, fT_4 normal

Overt hyperthyroidism

TSH ↓↓, fT_3/fT_4 ↑

Subclinical Hyperthyroidism – Definition and Prevalence

- Usually asymptomatic
- Grade 1: low (< 0.4 mU/L) serum TSH levels
- Grade 2: undetectable (< 0.1 mU/L) serum TSH levels
- Variable prevalence (0.7–1.8%)
- More common in women
- More common in older people
- 0,5%-7% annually progress to overt hyperthyroidism
- 5%-12% reversion to normal TSH levels

Ross et al. 2016

Subclinical Hyperthyroidism – Common Causes

Exogenous:

- Excessive thyroid hormone replacement therapy
- Intentional thyroid hormone suppressive therapy

Endogenous:

- Toxic multinodular goiter (especially in older persons)
- Graves' disease (especially in younger persons)
- Various forms of thyroiditis

Ross et al. 2016
Biondi 2015

Subclinical Hyperthyroidism – Clinical significance - risks

Bone

- Fractures ↑
- Osteoporosis ↑

Heart

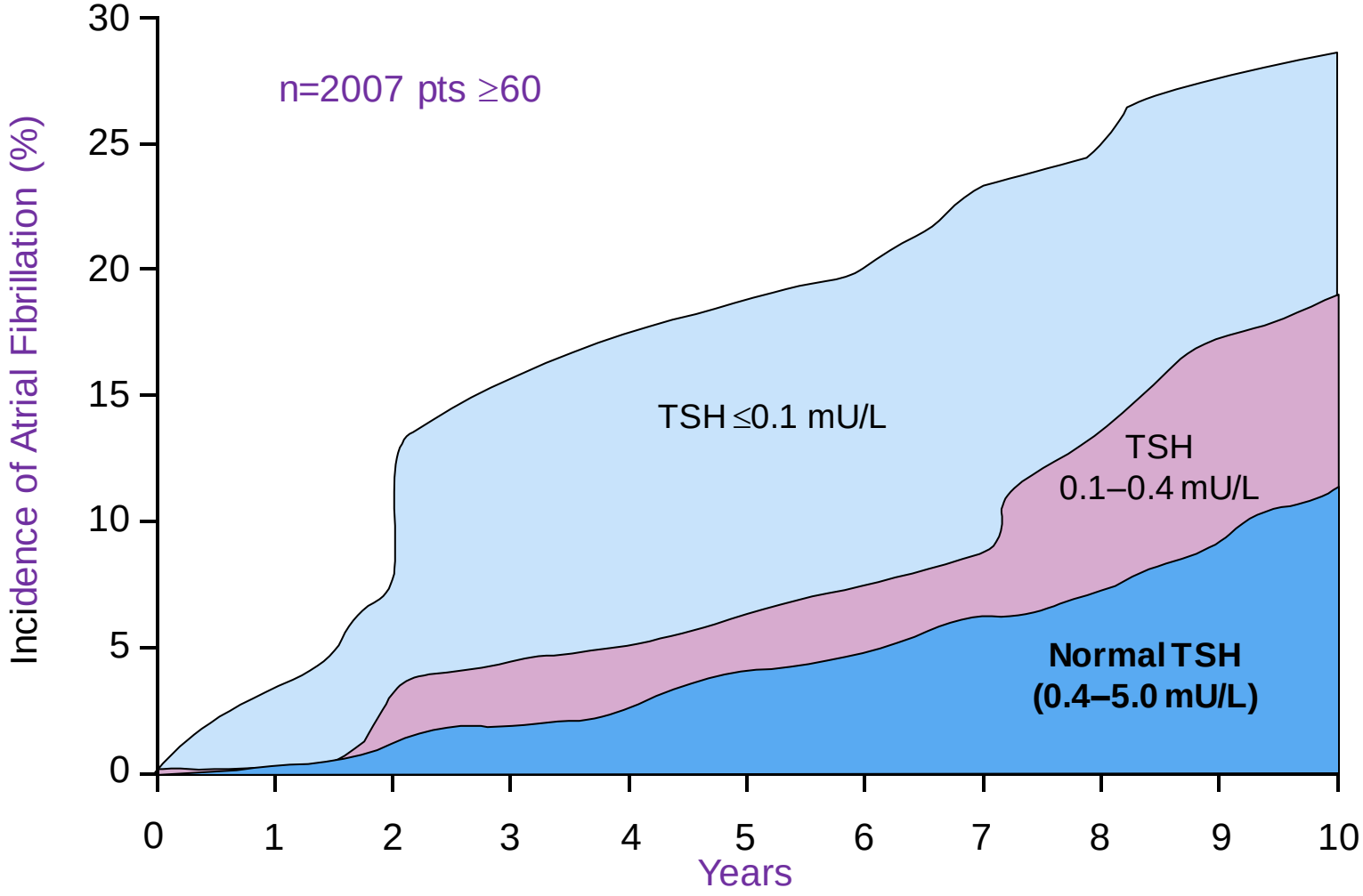
- Coronary heart disease ↑
- Cardiovascular mortality ↑
- Heart failure ↑
- Cardiac contractility ↑
- LV mass index ↑
- Atrial fibrillation ↑

Overall mortality ↑

Kahaly et al.2018

Ross et al. 2016

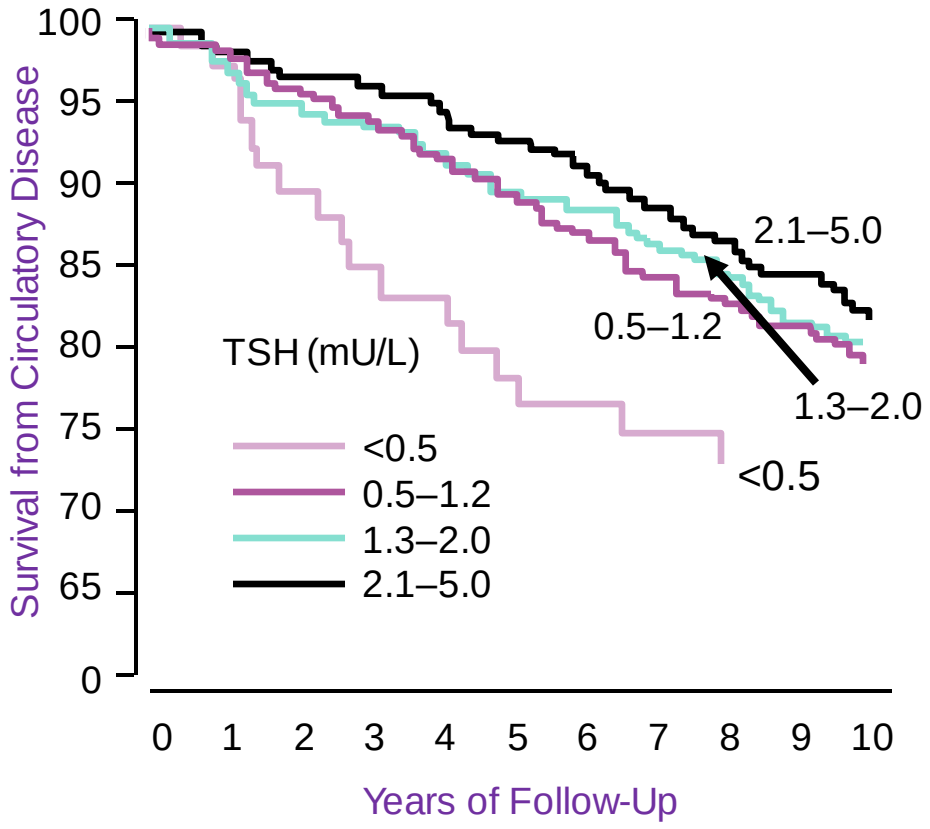
Consequences of Mild Thyrotoxicosis – Atrial Fibrillation



Adapted from: Sawin CT, et al. *N Engl J Med* 1994;331:1249–1252

Consequences of Mild Thyrotoxicosis – Cardiovascular Mortality

- 1191 UK persons
  - ≥60 years
  - No thyroid meds
- Assessments
  - Serum TSH in 1988–89
  - 10-year mortality
- Results
  - Low TSH in 6%
  - TSH correlated with CV mortality
  - Hazard ratio for TSH <0.5 at 2 years:
    - All-cause death: 2.1
    - CV death: 3.3



Parle JV, et al. *Lancet.* 2001;358:861–865

Subclinical Hyperthyroidism – Treatment

Because low TSH is often transient, careful monitoring is needed
(TSH, free T4, free T3)

Endogenous

When TSH is persistently <0.1 mU/L, treatment of SH is recommended :

- in all individuals ≥ 65 years of age
- in patients with cardiac risk factors, heart disease or osteoporosis
- in postmenopausal women who are not on estrogens or bisphosphonates
- in individuals with hyperthyroid symptoms

Treatment of SH should be considered when TSH is persistently <0.1 mU/L, in asymptomatic individuals <65 years of age without the risk factors listed above

Antithyroid medication is first choice of treatment
RAI and surgery are other options (depending of etiology)

Ross et al. 2016

Kahaly et al. 2018

Subclinical Hyperthyroidism – Treatment

Exogenous

- Careful titration of levothyroxine to maintain normal TSH
- Use smallest levothyroxine dose needed to meet therapeutic goals

Biondi 2015

Thyroid Disease

Hyperthyroidism and Pregnancy

INTRODUCTION :

— Overt hyperthyroidism is :

* relatively uncommon during pregnancy,

* occurring in 0.1 to 0.4 percent of all pregnancies .

* The diagnosis of pregnant women with hyperthyroidism parallels that of nonpregnant women and men but presents some unique problems.

The clinical manifestations, diagnosis, and causes of hyperthyroidism during pregnancy are presented here

Thyrotoxicosis in pregnancy: causes

- 85% Graves‘ disease → positive TSHR antibodies thyroid ultrasound
- thyroid autonomy → thyroid ultrasound
- gestational thyrotoxicosis → timing, negative TSAB
- thyrotoxicosis factitia, thyroiditis, thyroid hormone resistance

TSHR thyroid stimulating hormon receptor
TSAB thyroid stimulating antibody

Pregnancy complications

●**Overt hyperthyroidism** – Pregnancy complicated by poorly controlled overt hyperthyroidism (most often due to Graves' disease) is associated with increased rates of the following:

- Spontaneous abortion
- Premature labor
- Low birth weight
- Stillbirth
- Preeclampsia
- Heart failure

Overview of hyperthyroidism in pregnancy

- **Hyperthyroidism complicates about 0.2% of pregnancies**
- **Common symptoms:**
  - **Fatigue, tiredness, palpitations, heat intolerance, insomnia, proximal muscle weakness, shortness of breath, failure to gain weight (despite adequate calorie intake), tachycardia, Graves' ophthalmopathy (found in 1/3 of patients)**
- **Physical symptoms of pregnancy can also resemble those of thyrotoxicosis**
  - **E.g. palpitations, heat intolerance.**
- **Diagnosis: elevated fT_4 with decreased TSH**
- **Early changes in thyroid hormones during pregnancy (see above) can complicate the diagnosis of hyperthyroidism**

Bernstein PS, Koscica KL. Medscape Diabetes and Endocrinology 2003

Feto-maternal complications of thyrotoxicosis

mother

preeclampsia (up to 22%)*

heart failure (up to 60%) *

thyroid storm (up to 21%) *

side effects antithyroid drugs

child

hyperthyroidism

pre-term delivery (up to 88%) *

low birth weight (up to 23%) *

intrauterine death (up to 50%) *

congenital abnormalities

hydrops

goitre

drug induced hypothyroidism

Management of overt hyperthyroidism in pregnancy

Aim: fT4 upper normal range and <u>suppressed</u> TSH

- Propylthiouracil (PTU) is the treatment of choice when treatment is started in the first trimester
  - Concerns over hepatotoxicity (fulminant hepatic failure in 0.5% of patients)

- Switch from PTU to **methimazole (MMI)/thiamazole** **at the end of the 1st trimester**

- Avoid MMI during 1st trimester

  -Concern over risk of foetal abnormalities during this period (aplasia cutis, oesophageal atresia, delayed development)
  - If a patient is already receiving MMI, switch to PTU at start of pregnancy

- During breastfeeding only low doses up to 10 mg daily may be used without additional administration of Thyroid hormones

De Groot L et al. J Clin Endocrinol Metab, 2012;97: 2543-565; Bahn RS et al. J Clin Endocrinol Metab. 2012;97:2543-65.

Management of overt hyperthyroidism in pregnancy cont.

- ^{131}I is absolutely contraindicated in pregnancy

- propranolol 3-4 x (10-) 25-50 mg/d

- thyroid surgery: in 2. trimester only, if failure of antithyroid drugs or severe side effects,

monitor: TSH, fT4, blood count, liver enzymes (mother) and fetal development (ultrasound)

Management of fetal hyper- and hypothyroidism

- Need to treat: 0.01% of all pregnancies
- Confirmation through umbilical vein blood sampling

- **hypothyroidism**:

  reduce antithyroid drugs in mother
  (or intra-amniotic application of LT4)

- **thyrotoxicosis**:

  increase antithyroid drug dosage (for the mother)

Abalovich et al. Clinical Practice Guideline JCEM 2007

Methimaole – Pregnancy

- Untreated hyperthyroidism in pregnancy may lead to serious complications (e. g. thyroid storm, heart failure, intrauterine death, premature birth, malformations)
- Antithyroid drugs as well as maternal antibodies cross the placenta
- Methimazole is suspected to cause congenital malformations when administered during pregnancy, particularly in the first trimester of pregnancy and at high doses
- Repeated reports of partial aplasia cutis on the head, craniofacial malformations and a certain pattern of malformations (oesophageal atresia, ventricular sept defect)
- Thiamazole must only be administered during pregnancy after a strict individual benefit/risk assessment and only at the lowest effective dose without additional administration of thyroid hormones. Close maternal, fetal and neonatal monitoring is recommended

Abalovich et al. Clinical Practice Guideline JCEM 2007
MRP SPC Thyrozol 2019

Methimazol– Lactation

- methimazole passes into breast milk where it can reach concentrations corresponding to maternal serum levels, so that there is a risk of hypothyroidism developing in the infant.
- Breast-feeding is possible during thiamazole treatment; however, only low doses up to 10 mg daily may be used without additional administration of thyroid hormones
- The function of thyroid gland of the neonate has to be monitored regularly
- Thiamazole s recommended during lactation, given the concerns about PTU-mediated hepatotoxicity