Thyrotoxicosis, hyperthyroidism and hypothyroidism. Graves' disease, thyroiditis and thyroid nodules

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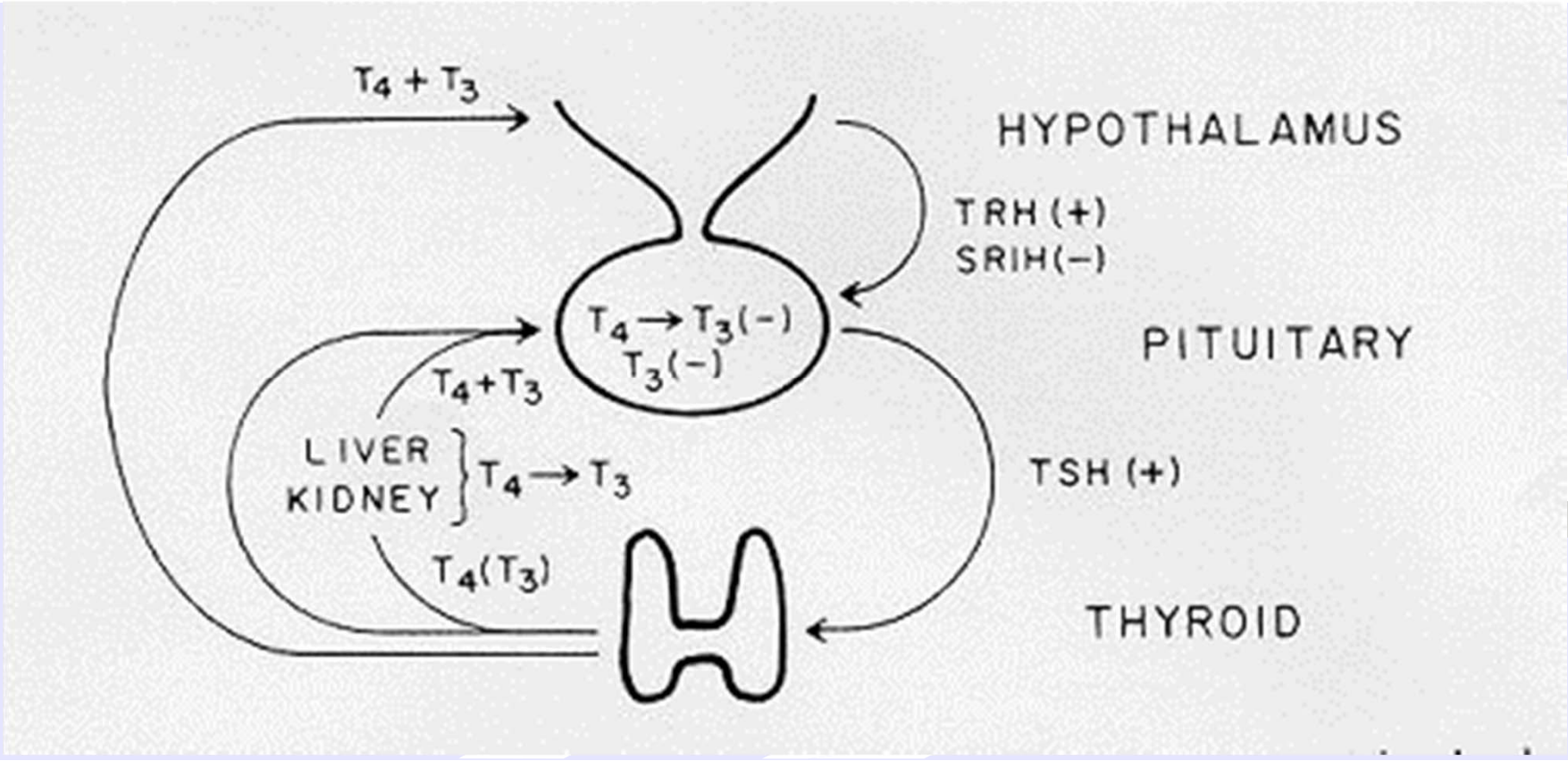
Thyroid hormones – synthesis and metabolism

- The synthesis of T4 (thyroxine) and T3 (triiodothyronine) involves trapping and oxidation of iodide (Na^+/I^-symporter), iodination of thyroglobulin (thyroid-peroxidase), digestion of thyroglobulin, and release of T3 and T4
- Free T4 (0.03%) and free T3 (0.3%) represent the active fraction; the remaining fraction is bound to thyroxine binding globulin (TBG) and albumin and is biologically inactive
- • T3 is 3-8x more potent, but T4 has a longer half-life
- • 85% of T4 is converted to T3 or reverse T3 (RT3) in the periphery by deiodinases (3 types)

Role of Thyroid Hormones

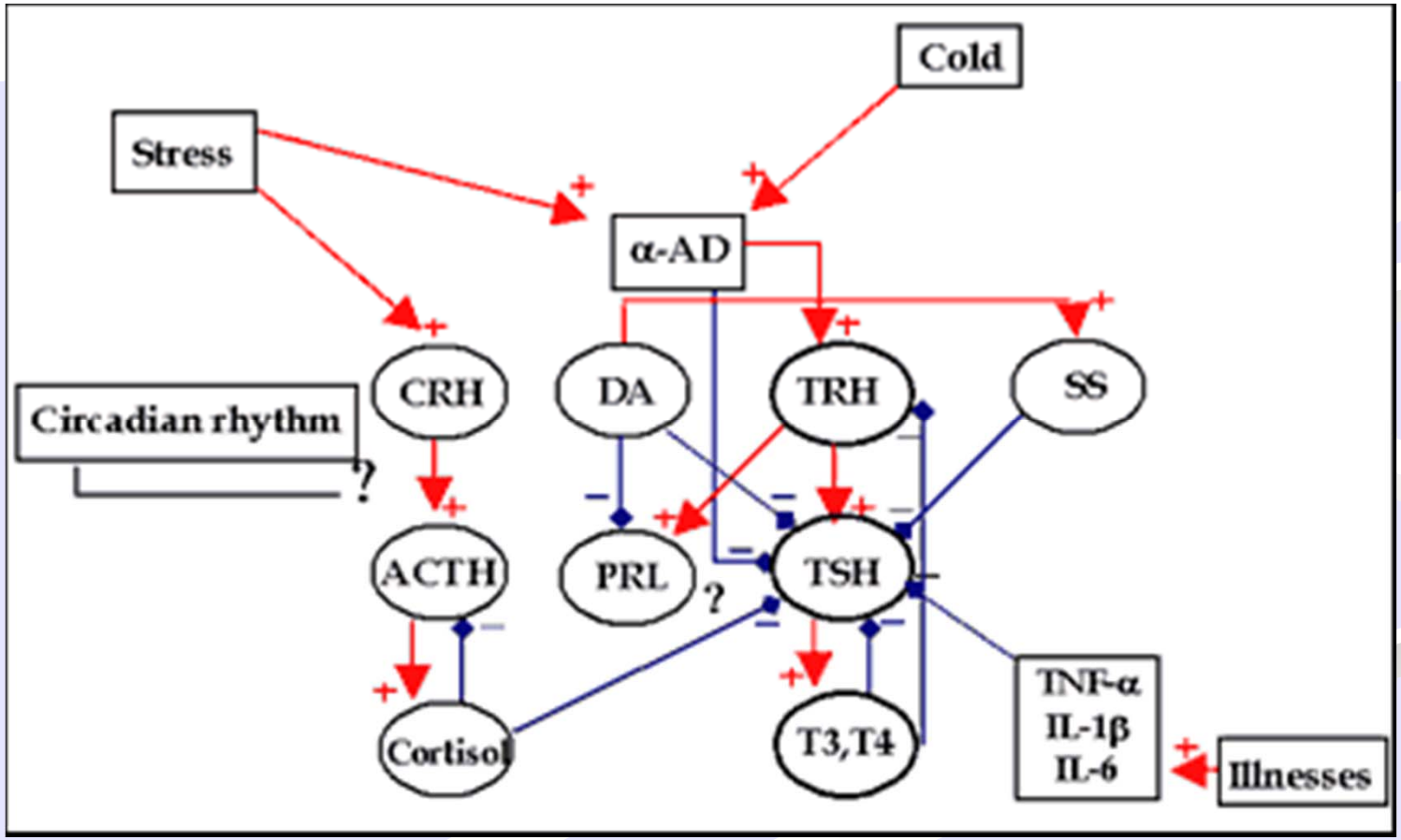
- • they act primarily through modifying gene transcription by binding to nuclear receptors
- • they increase the basal metabolic rate inducing increased Na+/K+ATP-ase activity, increased O_2 consumption, increased respiration, heat generation, and increased cardiovascular activity
- • they play a crucial role during fetal life in both neurological and somatic development

Hypothalamic-pituitary-thyroid axis
Negative feedback through fT_3



Neuroendocrine control of TSH secretion

Stress and cold as well as α-adrenergic signals stimulate TRH and TSH;
Severe illness, as well as dopamine and somatostatine suppress them



Prevalence of thyroid dysfunction in Bulgaria in 2006 (2402 participants)

Subgroups	Total (N=2402)	Females (N=1347)	Males (N=1055)
Euthyroid subjects (no history of thyroid disease)	90.0 %	87.6 %	93.2 %
Known hypothyroidism	2.2 %	3.6 %	0.5 %
Subclinical hypothyroidism	3.2 %	4.4 %	1.6 %
Overt hypothyroidism	0.9 %	1.0 %	0.9 %
Known hyperthyroidism	0.8 %	1.2 %	0.4 %
Subclinical hyperthyroidism	2.5 %	2.0 %	3.0 %
Overt hyperthyroidism	0.4 %	0.3 %	0.5 %

Centr Eur J Med 8(6):742-748

THYROTOXICOSIS / HYPERTHYROIDISM

Definition of thyrotoxicosis: Clinical syndrome due to excess of thyroid hormones in the periphery. **Hyperthyroidism** means only a hyperfunctioning thyroid gland (≠thyrotoxicosis). Thyrotoxicosis without hyperthyroidism is due e.g. do destruction

Disorder	TSH	Free T_4/T_3	Thyroid Antibodies	RAIU	Other
HYPERTHYROIDISM					
Graves' Disease	Decreased	Increased	TSI	Increased	Homogenous uptake on scan
Toxic Nodular Goitre	Decreased	Increased	None	Increased	Heterogeneous uptake on scan
Toxic Nodule	Decreased	Increased	None	Increased	Intense uptake in hot nodule on scan with no uptake in the rest of the gland
THYROIDITIS	With destruction and thyrotoxicosis without hyperthyroidism				
Subacute, Silent, Postpartum	Decreased	Increased	Up to 50% of cases	Decreased (increases once entering hypothyroid phase, when TSH rises)	In classical subacute painful thyroiditis, ESR increased
EXTRATHYROIDAL SOURCES OF THYROID HORMONE	= thyrotoxicosis without hyperthyroidism				
Endogenous (struma ovariae, ovarian teratoma, metastatic follicular carcinoma)	Decreased	Increased	None	Decreased	
Exogenous (drugs)	Decreased	Increased (T_4 would be decreased if taking T_3)	None	Decreased	

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Symptoms of thyrotoxicosis

- Intolerance to heat, sweating (hot profuse sweat)
- Increased appetite with weight loss (> 3 kg for one month), frequent defecation,
- Restlessness, easy fatigability, insomnia
- *Palpitations* (constantly high pulse rate), dyspnea on exertion, oedema, high systolic BP
- Menstrual abnormalities in women (hypo- and oligomenorrhea)

Clinical examination - signs

- Increased heart rate at rest > 100/min. (e.g. after 5 min rest)
- “velvet skin"
- Tremor of the hands when eyes closed and fingers widely spread
- Positive eye symptoms (Dalrymple, Graeffe, Gauffrois); signs of thyroid ophthalmopathy (paresis of ocular muscles; periorbital edema; conjunctival inection)
- Cardiac murmur – a systolic murmur on a broad area
- *Arterial blood pressure* – a tendency to lower diastolic (≤ 60 mm Hg) and higher systolic blood pressure(≥ 140 mm Hg)
- *Thyroid gland palpation*

Clinical signs and symptoms – summary

Most common differential diagnosis – anxiety / panic disorders, and the perimenopause

General	**Fatigue, heat intolerance, irritability, fine tremor**
CVS	Tachycardia, atrial fibrillation, palpitations Elderly patients may have only cardiovascular symptoms, commonly new onset atrial fibrillation
GI	Weight loss with increased appetite, thirst, increased frequency of bowel movements (hyperdefecation)
Neurology	Proximal muscle weakness, hypokalemic periodic paralysis (more common in Asians)
GU	Oligomenorrhea, amenorrhea, decreased fertility
Dermatology	Fine hair, skin moist and warm, vitiligo, soft nails with onycholysis (Plummer's nails), palmar erythema, pruritis Graves' disease: clubbing (acropachy), pretibial myxedema (rare)
MSK	Decreased bone mass, proximal muscle weakness
Hematology	Graves' disease: leukopenia, lymphocytosis, splenomegaly, lymphadenopathy (occasionally)
Eye	Graves' disease: lid lag, retraction, proptosis, diplopia, decreased acuity, puffiness, conjuctival injection

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Absolute indications for the measurement of thyroid hormones

- Diagnosis of overt and subclinical forms of thyrotoxicosis and hypothyroidism
- Suspicion of thyroid-associated ophthalmopathy (TAO, Graves' ophtalmopathy)
- Follow-up and titration of antithyroid drugs (ATD) or replacement therapy with Levothyroxine
- Neonatal screening for hypothyroidism
- Arrhythmia (especially supraventricular one)
- Older people (>60 years) with depression or dementia

Relative indications for evaluation of thyroid hormones

- Presence of *other autoimmune diseases* (polyglandular autoimmune syndromes): diabetes mellitus type 1, Addison's disease, primary hypogonadism, pernicious anemia, vitiligo, collagenoses and others.
- *After child-birth* (up to the 3rd month) – if history of a thyroid autoimmune disease is positive. Postpartal thyroiditis is seen in up to 20% of women with Hashimoto.
- Children with impaired mental or physical development

Measuring thyroid hormones TSH and freeT_4

	TSH	Free T4, T3
Overt thyrotoxicosis	↓	↑
Subclinical hyperthyroidism or non-thyroidal causes	↓	normal
Primary overt hypothyroidism	↑	↓
Primary subclinical hypothyroidism or non-thyroidal causes	↑	normal
Secondary hypothyroidism (pituitary failure)	↓ or normal	↓

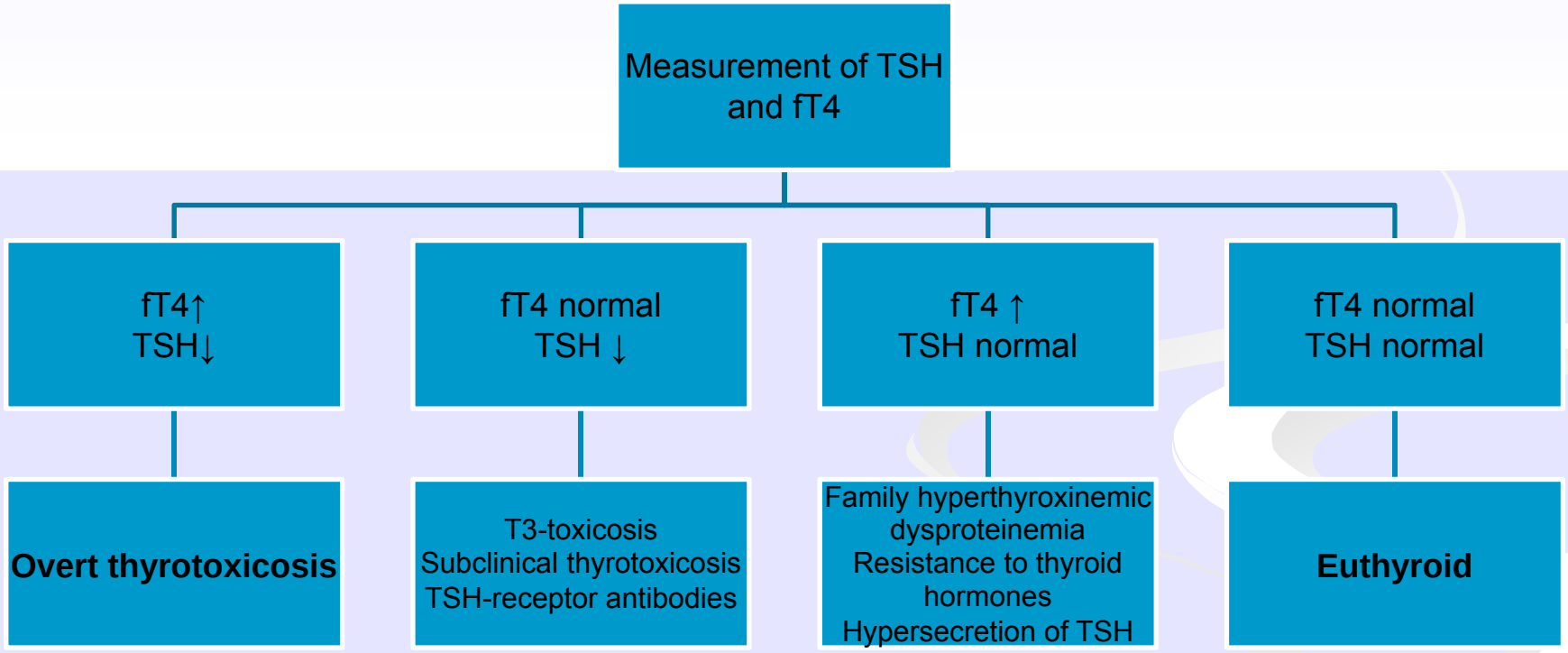
TSH, fT4 or fT3 ?

- Measurement of TSH and fT4 is usually optimal
- TSH-measurement is sufficient for screening if the thyroid gland is the culprit (not the pituitary!)
- *fT3* is measured if:
- Decreased conversion of T4 to T3 is suspected (*low T3* syndrome, deiodinase defects)
- Isolated T3-toxicosis possible (nodular hyperplasia, recurrence of Graves' disease)
- The thyroid function tests are unusual

Differential diagnosis of decreased serum TSH

- *Hyperthyroidism* (most common) – autoimmune (Graves' disease, Hashimoto's thyroidits) or autonomous (multiple nodules or toxic adenoma)
- Secondary or tertiary hypothyroidism (impaired pituitary or hypothalamic secretion)
- Thyreotoxicosis factitia – treatment with supraphysiological doses of levothyroxine
- Fasting (anorexia) or severe systemic diseases (protection from catabolism) = non-thyroidal euthyroid sick syndrome
- Depression, psychosis
- Treatment with: glucocorticoids, beta-blockers, opiates, serotonin agonists and antagonists
- Pregnancy

DD thyrotoxicosis

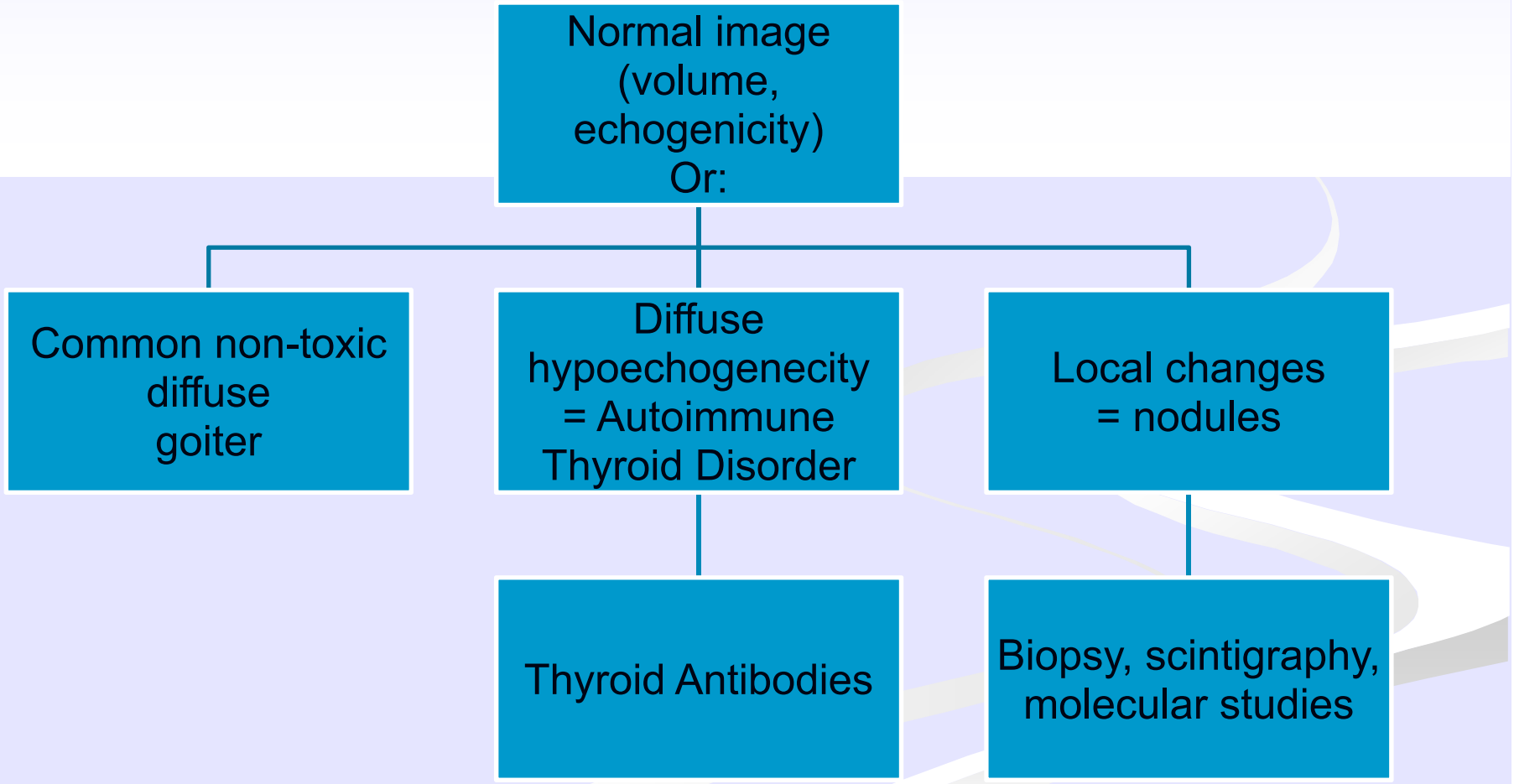


Common thyroid tests besides hormones

- **TSH, fT4**
- Palpation and neck **ultrasound** (diagnosis of autoimmune disease or nodules)
- Thyroid **antibodies** – if autoimmune cause suspected: thyroid-peroxidase Ab (TPOAb); thyroglobulin Ab (TgAb); TSH-receptor Ab (TRAb)
- **Fine-needle biopsy** of the thyroid – for cytological evaluation of nodular changes
- **Nuclear imaging** (scintigraphy, SPECT-CT) if needed

Role of thyroid ultrasound

Diagnosis of diffuse (autoimmune disease) or focal changes (nodules)



Positive antibodies in autoimmune thyroid disease (AITD)

% of patients with positive antibody levels	TgAb	TPOAb	TRAb
Graves' disease	20%	70%	90%
Hashimoto's thyroiditis	50%	85%	< 5%

TRH-test – NOT USED ANYMORE

- **Lack of elevation of TSH after stimulation with Thyrotropin-releasing hormone due to**:
- *Suppressed secretion* – usually in subclinical thyrotoxicosis (subtle excess of thyroid hormones or T3-toxicosis) or presence of high levels of TRAb.
- Pituitary tissue does not respond to stimulation – *secondary (pituitary) hypothyroidism* with damage of the pituitary gland

Graves' disease

- Definition: an autoimmune disorder characterized by stimulating antibodies to the TSH-receptor that leads to hyperthyroidism
- Epidemiology:
- - most common cause of thyrotoxicosis in younger people
- -peak in the 3rd and 4th decade
- - Female/male ratio = 7:1 (1-2 % of women)
- -Familial predisposition, association with HLAB8 and DR3
- - May be associated with other eutoimmune diseases: pernicious anemia, type 1 diabetes, Addisson,s disease etc.

Graves' disease

- Clinical features:
  - - signs and symptoms of thyrotoxicosis + diffuse elastic goiter
  - - In 1/3 - ophtalmopathy (Graves'ophtalmopathy, GO)
  - - Rarely dermopathy (pretibial myxedema, non-pitting edema)
- Investigations:
  - - low TSH, increased fT4 and T3,
  - - homogenous hypoechogenicity on US with increased Doppler signals,
  - - positive TRAb (other thyroid Abs may also be +),
  - - increased radioiodine uptake, homogenous thyroid scan

Diagnostic algorithm in Graves' disease

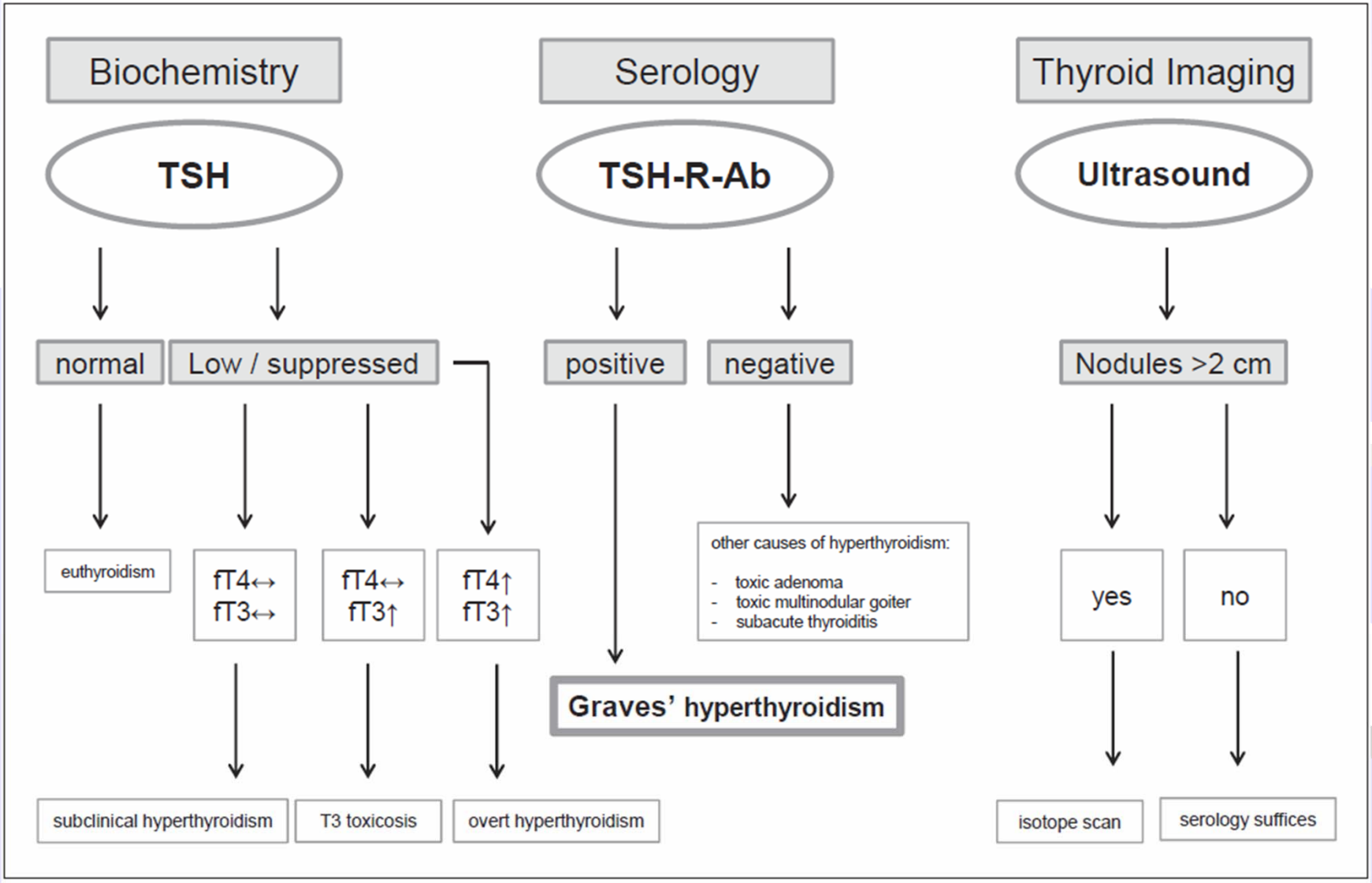


Fig. 1. Algorithm for investigating a patient with suspected Graves' hyperthyroidism. *Eur Thyroid J 2018;7:167–186*

Graves' disease – treatment with ATD

- Antithyroid drugs (ATD) = thionamides: propylthiouracil (PTU) or methimazole (MMI)
- ■ PTU and MMI inhibit thyroid hormone synthesis by inhibiting peroxidase-catalyzed reactions, organification of iodide, blocking the coupling of iodotyrosines
- ■ PTU also inhibits peripheral conversion of T4 to T3
- ■ continue treatment until remission occurs (20-40% of patients achieve spontaneous remission at 6-18 mo of treatment)
- ■ small goitre and recent onset are good indicators for long-term remission with ATD
- ■ major side effects: hepatitis, agranulocytosis, and fever/arthralgias
- ■ minor side effects: rash

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Antithyroid drugs (MMI vs PTU)

	MMI	PTU
Absorption	rapid	rapid
Bioavailability	~100%	~100%
Peak serum level	60–120 min	60 min
Serum half-life	6–8 h	90 min
Thyroid concentration	5×10^5 mol/L	unknown
Thyroid turnover	slow	moderate
Duration of action	>24 h	8–12 h
Serum protein binding	nil	>75%
Crosses placenta	++	+
Levels in breast milk	++	+
Volume of distribution	40 L	20 L
Excretion	renal	renal
Metabolism during illness		
Renal	nil	nil
Liver	prolonged	nil
Potency	10×	1×
Normalization T3/T4	6 weeks	12 weeks
Adverse events	15%	20%
Agranulocytosis	0.6%	1–1.5%
Cross-reaction of adverse events	13.8%	15.2%
Compliance	high	fair
Costs	low	moderate

MMI, methimazole; PTU, propylthiouracil.

Table 3. Adverse events of antithyroid drugs

Common (1.0–5.0%)
Skin rash
Urticaria
Arthralgia, polyarthritis
Fever
Transient mild leukopenia
Rare (0.2–1.0%)
Gastrointestinal
Abnormalities of taste and smell
Agranulocytosis

Eur Thyroid J 2018;7:167–186

Graves' disease – treatment with ATD and radioiodine

- ■ MMI preferred vs. PTU due to longer duration of action (once daily for most), more rapid efficacy, better safety
- ■ in pregnancy: use PTU during first trimester and MMI during second and third trimester.

- • symptomatic treatment with β-blockers
- • thyroid ablation with **radioactive 131I if PTU or MMI trial does not produce disease remission**
- ■ high incidence of hypothyroidism after 131I requiring lifelong thyroid hormone replacement
- ■ contraindicated in pregnancy
- ■ may worsen ophthalmopathy

Graves' disease - thyroidectomy

- • Subtotal or total thyroidectomy (indicated for large goitres, suspicious nodule for Ca, if patient is intolerant to thionamides and refusing RAI ablation)
- ■ risks include hypoparathyroidism and vocal cord palsy

Treatment of thyrotoxicosis in Graves' disease – other medical options

- Glucocorticoids – in severe hyperthyroidism or thyroid storm (inhibit the peripheral conversion of T4 to T3)
- Lithium – second line treatment blocking thyroid hormone release
- Sodium perchlorate – second line treatment (blocking the sodium/iodine symporter; toxicity!)

Management of Graves' disease

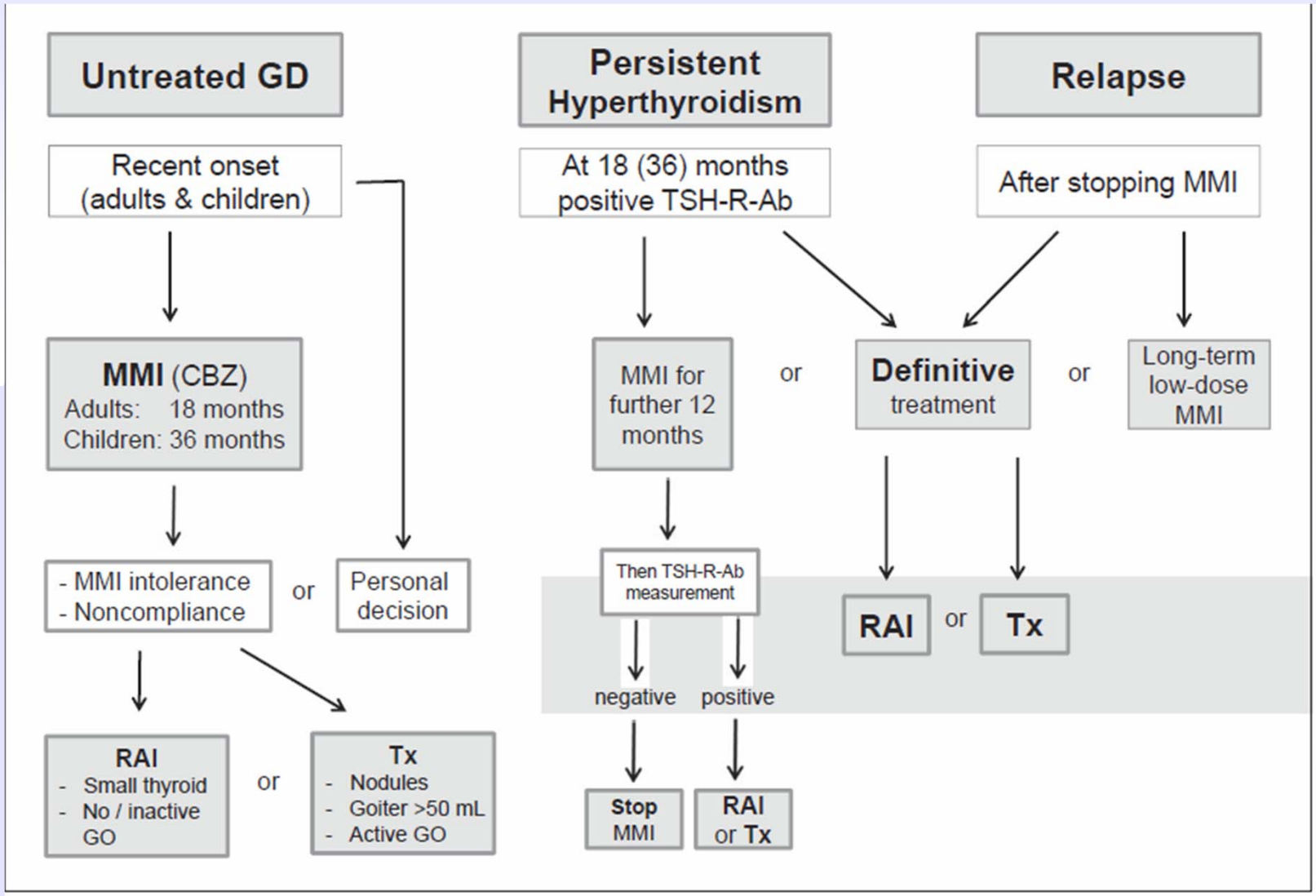


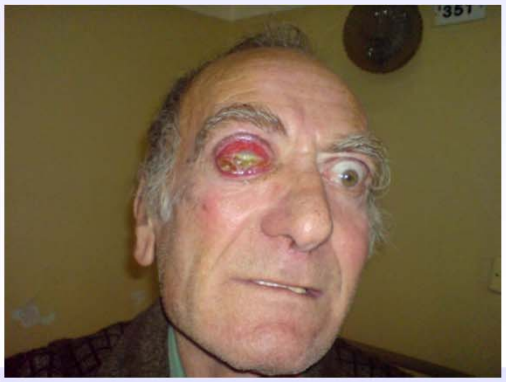
Fig. 2. Algorithm for the management of a patient with Graves' hyperthyroidism. GD, Graves' disease; MMI, methimazole; CBZ, carbimazole; GO, Graves' orbitopathy; RAI, radioactive iodine; Tx, total thyroidectomy.

Eur Thyroid J 2018;7:167–186

Graves' ophtalmopathy
(TSH-R-Ab usually +; severe / active forms treated)

GO severity: NO SPECS score

0. No symptoms or signs of GO
1. Only signs, no symptoms
2. Soft tissue involvement (aperture in mm)
3. Proptosis (Hertel in mm)
4. Extraocular muscle involvement (motility, double vision)
5. Corneal involvement
6. Sight loss (visual acuity, colour vision)



GO activity assessment according CAS

1 Spontaneous retrobulbar pain
2 Pain on attempted upward or downward gaze
3 Redness of eyelids
4 Redness of conjunctiva
5 Swelling of caruncle or plica
6 Swelling of eyelids
7 Swelling of conjunctiva (chemosis)

* Inactive GO = CAS <3
* Active GO = CAS ≥3

GO severity assessment according to EUGOGO

* Mild GO
  Patients whose features of GO have only a minor impact on daily life insufficient to justify immunosuppressive or surgical treatment. They usually have one or more of the following: minor lid retraction (<2 mm), mild soft-tissue involvement, exophthalmos <3 mm above normal for race and gender, no or intermittent diplopia and corneal exposure responsive to lubricants
* Moderate-to-severe GO
  Patients without sight-threatening GO whose eye disease has sufficient impact on daily life to justify the risks of immunosuppression (if active) or surgical intervention (if inactive). They usually have two or more of the following: lid retraction ≥2 mm, moderate or severe soft-tissue involvement, or exophthalmos ≥3 mm above normal for race and gender, inconstant or constant diplopia
* Sight-threatening GO (very severe GO)
  Patients with DON and/or corneal breakdown

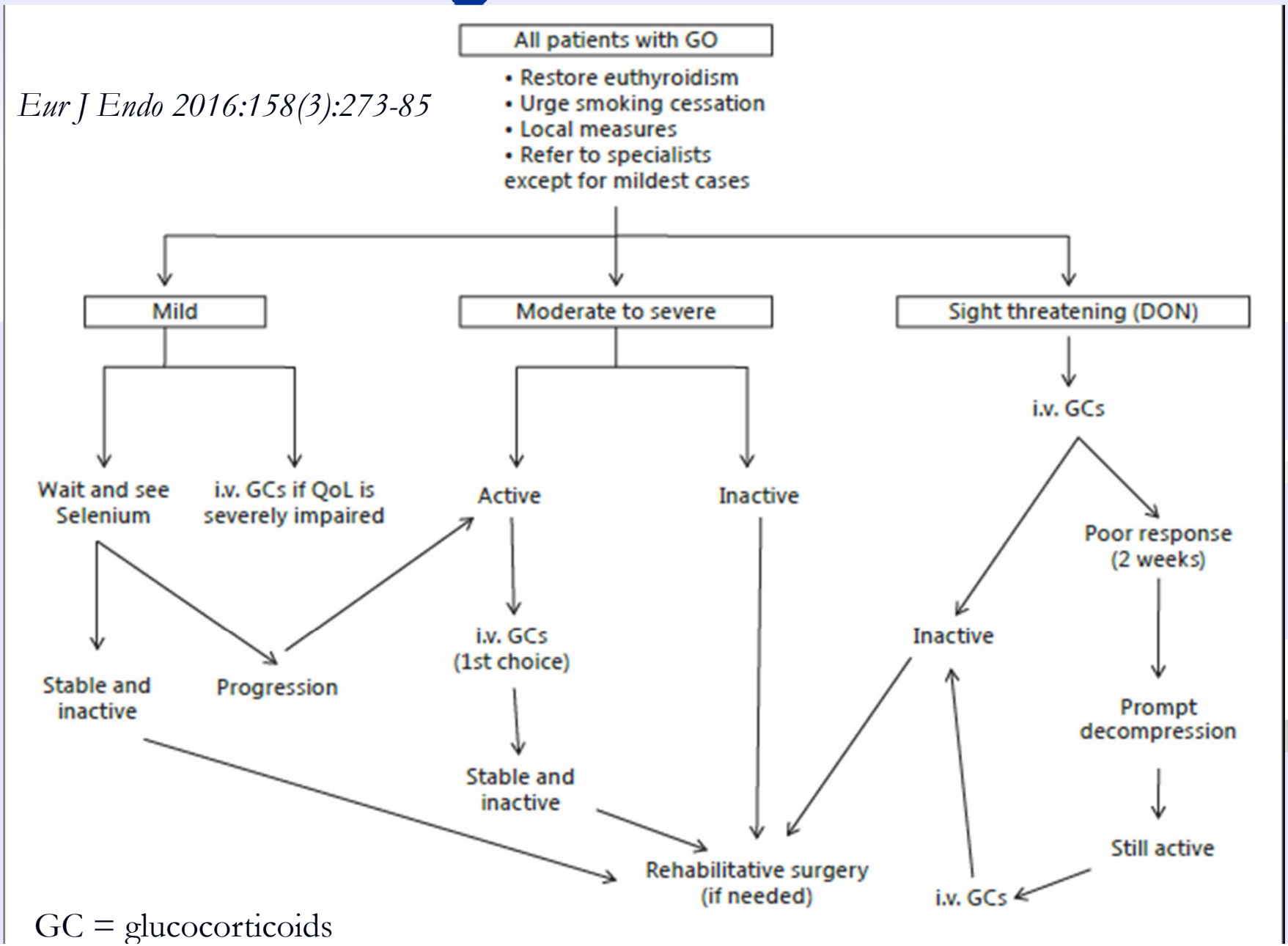
Eur Thyroid J 2018;7:167–186
Eur Thyroid J 2016;5:9-26

Basic treatment of GO

- Restore and support stable euthyroidism
- ■ smoking cessation is important
- ■ prevent drying of eyes
- ■ high dose prednisone in severe cases
- ■ orbital radiation, surgical decompression

Management of GO

Eur J Endo 2016:158(3):273-85



GC = glucocorticoids

Toxic (=hyperthyroid) nodules - treatment

- **Etiology**: autonomous hormone production from a single (toxic adenoma) or multiple nodules (toxic multinodular goiter)
- Clinical **features**: goiter with nodular changes; tachycardia, heart failure, arrhytmia, weight loss, nervousness, tremor, sweats; rarely eye symptoms
- **Lab tests**: low TSH, high T3 and T4; increased RAI-uptake in nodules; typical US image, negative Abs
- **Treatment**: Initiate ATD to restore euthyroidism (preferably MMI); then definitive treatment: surgery or RAI-ablation; non-invasive ablation also possible (laser, radio-frequency, high intensity focused ultrasound)

Advantages and disadvantages of total thyroidectomy

Advantages	Disadvantages
No recurrent hyperthyroidism	Risk of postoperative hypoparathyroidism
No radiation risk	Risk of recurrent nerve palsy
Rapid control of hyperthyroidism	Permanent hypothyroidism
No reported detrimental effect on the course of Graves' orbitopathy	Risks related to anesthesia or surgery
	Hospitalization
	Costs
	Permanent scar

Subclinical hyperthyroidism

(supressed TSH with normal fT4 and fT3)

Etiology

- Usually – **Autonomous nodules** – toxic adenoma / multinodular goiter in older people
- **Graves' disease** in younger persons
- Hashimoto's thyroiditis / Postpartum thyroiditis thyroiditis;
- Subacute thyroiditis (de Quervain)
- Overdosage of thyroid hormones
- Amiodarone and iodinated contrast agents

Consequences of subclinical hyperthyroidism

- Subtle **psychic disorders** – dominantly affective disorders
- Elevated risk of **postmenopausal osteoporosis and fractures**
- **Heart problems**: diastolic and systolic dysfunction, atrial extrasystoles and arrhythmias; heart failure; CV-events and death
- **Clinical presentation** – most often tremor, palpitations, fatigue

Eur Thyroid J 2015;4:149–163

Work-up in subclinical hyperthyroidism

Level I To establish the diagnosis of persistent SHyper	Level II To establish the aetiology of SHyper	Level III To establish the risks associated with SHyper and appropriate treatment
TSH (initial screening) FT_4, TT_3 or FT_3 (if serum TSH is low)	Thyroid ultrasonography[1] Thyroid scan and possibly thyroid radioiodine uptake TSHR-Abs[2]	CT, MRI[3] ECG[4], Holter ECG[5], Doppler echocardiography[6] BMD[7]

[1] Ultrasonography can guide fine needle aspiration biopsy in cases of suspicious hypofunctioning thyroid nodules in nodular goitres. [2] TSH-receptor antibodies (TSHR-Abs) can be useful to identify autoimmune SHyper. [3] Computed tomography (CT) or magnetic resonance imaging (MRI) should be used in selected patients to assess airway compression. [4] ECG should be considered in symptomatic patients. [5] Holter ECG is useful to assess atrial arrhythmias. [6] Doppler echocardiography is recommended in patients with AF, CHD or HF and/or underlying heart disease. [7] BMD should be evaluated in postmenopausal patients, in elderly patients and in patients with underlying bone risk factors.

Eur Thyroid J 2015;4:149–163

Treatment of subclinical hyperthyroidism is obligatory > 65 yrs as well in younger symptomatic patients

- **Without ATD** – beta-blockers, antiresoptive bone active agents
- **Be Careful with replacement treatment with levothyroxine**
- **Treatment with ATD, surgery or RAI**



Thyrotoxic crisis (thyroid storm)

- **Definition**: acute exacerbation of thyrotoxicosis presenting in a life-threatening state secondary to uncontrolled hyperthyroidism – medical emergency!
- • rare, but serious with mortality rate between 10-30%
- **Etiology and Pathophysiology**
- • often precipitated by infection, trauma, or surgery in a hyperthyroid patient
- **Differential Diagnosis**
- • sepsis, pheochromocytoma, malignant hyperthermia, drug overdose, neuroleptic malignant syndrome

Thyrotoxic crisis (thyroid storm)

- **Clinical Features**
- • hyperthyroidism
- • extreme hyperthermia (≥40°C), tachycardia, vomiting, diarrhea, vascular collapse, hepatic failure with jaundice, and confusion
- • tachyarrhythmia, CHF, shock
- • mental status changes ranging from delirium to coma

- **Laboratory Investigations**
- • increased free T3 and T4, undetectable TSH
- • ± anemia, leukocytosis, hyperglycemia, hypercalcemia, elevated LFTs

Thyroid storm – point scale for diagnosis

Criteria	*Points*	*Criteria*	*Points*
Thermoregulatory dysfunction		Gastrointestinal–hepatic dysfunction	
Temperature (°F)[b]		Manifestation	
99.0–99.9	5	Absent	0
100.0–100.9	10	Moderate (diarrhea, abdominal pain, nausea/vomiting)	10
101.0–101.9	15	Severe (jaundice)	20
102.0–102.9	20		
103.0–103.9	25		
≥104.0	30		
Cardiovascular		Central nervous system disturbance	
Tachycardia (beats per minute)		Manifestation	
100–109	5	Absent	0
110–119	10	Mild (agitation)	10
120–129	15	Moderate (delirium, psychosis, extreme lethargy)	20
130–139	20	Severe (seizure, coma)	30
≥140	25		
Atrial fibrillation			
Absent	0		
Present	10		
Congestive heart failure		Precipitant history	
Absent	0	Status	
Mild	5	Positive	0
Moderate	10	Negative	10
Severe	20		

Scores totaled	
>45	Thyroid storm
	Impending storm
<25	Storm unlikely

[a]Source: Burch and Wartofsky (26). Printed with permission.
[b]Celsius 37.2–37.7 (5), 37.8–38.3 (10), 38.3–38.8 (15), 38.9–39.4 (20), 39.4–39.9 (25), ≥40 (30 points).

Thyrotoxic crisis (thyroid storm)

- **General Measures**
- • fluids, electrolytes, and vasopressor agents as indicated
- • a cooling blanket and acetaminophen can be used to treat the pyrexia
- • propranolol or other β-blockers that additionally decrease peripheral conversion of T3 → T4, but should be used with caution in CHF patients as it may worsen condition

Thyrotoxic crisis (thyroid storm)

- **Specific Measures**
- • **PTU** is the drug of choice and is used in high doses
- • Give **iodide**, which acutely inhibits the release of thyroid hormone, one hour after the first dose of PTU
- ■ Sodium iodide 1 g IV drip
- OR
- ■ Lugol's solution 2-3 drops 3 times daily
- OR
- ■ Potassium iodide (SSKI) 5 drops 3 times daily • **Glucocorticoids** e.g. dexamethasone 2-4 mg IV every 6h for the first 24-48 hours; lowers body temperature and inhibits conversion of T3 → T4

Treatment of thyroid storm (our experience)

First-choice medical treatment : **Methizol 50-100 mg** or **PTU 500-1000 mg via the gastric tube**

Glucocorticoids: -initially 1 mg Methylprednisolone/kg body weight i.v., then the same dose - in a 24-hour infusion

Additional medical treatment:

Continuous infusion with heparin for prophylaxis of thrombosis; targeted partial thromboplastin time 1,5 to twice above reference ranges.

Other measures:

Saline infusions (4-6 l/24h.)

Parenteral nutrition

Hyperthermia treatment with physical measures (sacks with ice)

Antibacterial treatment on suspicion of bacterial infection

Common measures (decubitus prophylaxis, tracheal toilet)

Dialysis (if life-threatening situation with very high hormone levels)

Adding beta-blocker to treatment is done cautiously nowadays because tachycardia is necessary for maintenance of high minute volume. Unselective beta-blockers are preferred, e.g. **Propranolol**, as the extracardial action is targeted.

Prognosis • <20% mortality rate if rapidly recognized and treated

HYPOTHYROIDISM

Hypothyroidism

- Definition: clinical syndrome caused by insufficient thyroid hormone production
- Epidemiology
- • 2-3% of general population; F:M = 10:1
- • up to 10-15% of women over age 50 have subclinical hypothyroidism (normal T4, TSH mildly elevated)
- • most common causes: Hashimoto’s disease and thyroidectomy; iodine deficiency most common cause worldwide

Hypothyroidism - etiology

- • **primary hypothyroidism** (90%)
- ■ **<u>iatrogenic: post-ablative (131I or surgical thyroidectomy</u>**)
- ■ **<u>autoimmune: Hashimoto's thyroiditis</u>**, chronic thyroiditis, idiopathic, burnt out Graves'
- ■ hypothyroid phase of subacute thyroiditis
- ■ drugs: goitrogens (iodine), PTU, MMI, lithium
- ■ infiltrative disease (progressive systemic sclerosis, amyloid)
- ■ iodine deficiency
- ■ congenital (1/4,000 births)
- ■ neoplasia

Hypothyroidism - etiology

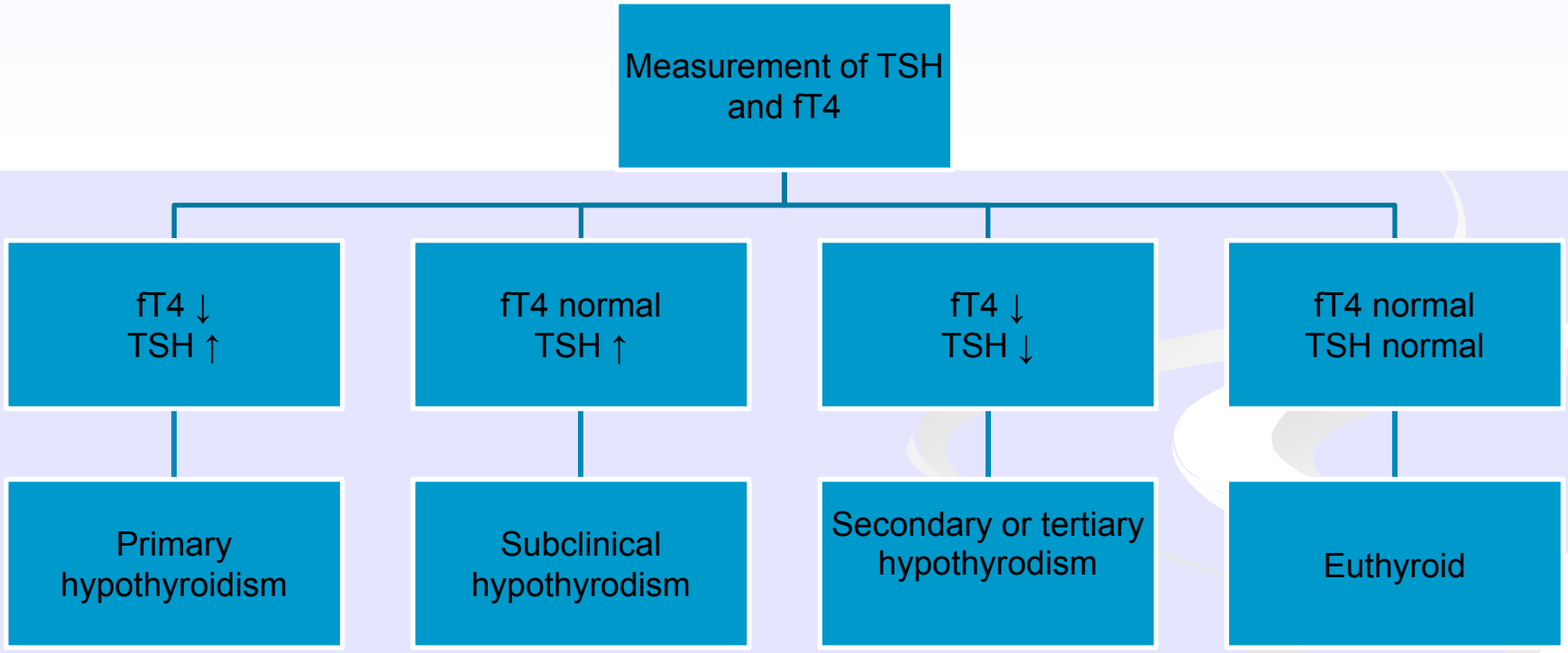
- • **secondary hypothyroidism**: pituitary hypothyroidism
- ■ insufficiency of pituitary TSH
- • **tertiary hypothyroidism**: hypothalamic hypothyroidism
- ■ decreased TRH from hypothalamus (rare)
- ■ decreased TRH from hypothalamus (rare)
- • **resistance to thyroid hormone** (Refetoff syndrome)

Hypothyroidism – clinical features

General	Fatigue, cold intolerance, slowing of mental and physical performance, hoarseness, macroglossia
CVS	Pericardial effusion, bradycardia, hypotension, worsening CHF + angina, hypercholesterolemia, hyperhomocysteinemia, myxedema heart
Respiratory	Decreased exercise capacity, hypoventilation secondary to weak muscles, decreased pulmonary responses to hypoxia, sleep apnea due to macroglossia
GI	Weight gain despite poor appetite, constipation
Neurology	Paresthesia, slow speech, muscle cramps, delay in relaxation phase of deep tendon reflexes ("hung reflexes"), carpal tunnel syndrome, asymptomatic increase in CK, seizures
GU	Menorrhagia, amenorrhea, impotence
Dermatology	Puffiness of face, periorbital edema, cool and pale, dry and rough skin, hair dry and coarse, eyebrows thinned (lateral 1/3), discolouration (carotenemia)
Hematology	Anemia: 10% pernicious due to presence of anti-parietal cell antibodies with Hashimoto's thyroiditis

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Diff. Diagnosis Hypothyroidism



Differential diagnosis of elevated TSH

- Primary hypothyroidism
- Iodine–deficiency (rare in Bulgaria)
- Treatment with iodine, lithium, antiestrogens (Clomiphene), spironolactone, dopamine-receptor blockers (antipsychotics), some H2-blockers (cimetidine, ranitidine)
- TSH-secreting pituitary tumors or resistance to thyroid hormones – very rare

Hypothyroidism – treatment

- Levothyroxine (dose range: 0.05-0.2 mg PO OD ~1.6 µg/kg/d)
- • elderly patients and those with CAD: start at 0.025 mg daily and increase gradually every 6 weeks (“start low, go slow”)
- • after initiating Levthyroxine, TSH needs to be evaluated in 6 wk; dose is adjusted until TSH returns to normal
- • once maintenance dose achieved, follow-up TSH with patient annually
- • if secondary/tertiary hypothyroidism - monitor via measurement of free T4 (TSH unreliable in this setting)

Levothyroxine replacement treatment

- The general goal is TSH < 4.2 mUI/L;
- In older and plurimorbid patients < 10 mUI/L;
- In young fertile women < 2.5 mUI/L
- The absorption of L-T4 is decreased by other drugs: bisphosphonates, proton-pump inhibitors, calcium and iron salts, caffeine and others
- Should be taken in the fasting state with water only

Hashimoto’s thyroiditis

- • most common form of primary hypothyroidism in BG
- • chronic autoimmune thyroiditis due to both cellular and humoral factors destroying the thyroid tissue
- • two major forms: goitrous and atrophic; both forms share same pathophysiology but differ in the extent of lymphocytic infiltration, fibrosis, and thyroid follicular cell hyperplasia
- • goitrous variant usually presents with goiter and euthyroidism, then hypothyroidism becomes evident
- • atrophic variant patients are hypothyroid from the start
- Rarely – thyrotoxicosis as a start (Hashitoxicosis)

Hashimoto's thyroiditis

- Etiology and Pathophysiology
- • defect in clone of T-suppressors leads to cell-mediated destruction of thyroid follicles
- • B lymphocytes produce antibodies against thyroid components including thyroglobulin, thyroid peroxidase, TSH receptor, Na+/I– symporter

- Risk Factors
- • female gender (F:M = 7-8:1)
- • genetic susceptibility: increased frequency in patients with Down's syndrome, Turner's syndrome, certain HLA alleles, cytotoxic T-lymphocyte-associated protein 4 (CTLA-4)
- • family Hx or personal Hx of other autoimmune diseases
- • cigarette smoking
- • high iodine intake
- • stress and infection

Hashimoto's thyroiditis

- Diagnosis (2 of three):

- Hypothyroidism (not obligatory)
- Diffuse heterogenous hypoechogenicity on US
- Positive thyroid Abs (TPOAb and/or TgAb)

- In difficult cases measure TRAb (to exclude Graves') or perform FNA-biopsy (to exclude simple nodules or neoplasms)

Hashimoto’s thyroiditis

- Treatment – not needed if euthyroid
- Levothyroxine replacement – if hypothyroid
- Short-term treatment with ATD – if hyperthyroid

Myxedema coma

- Definition
- • severe hypothyroidism complicated by trauma, sepsis, cold exposure, MI, inadvertent administration of hypnotics or narcotics, and other stressful events – medical emergency!
- • rare, high level of mortality when it occurs (up to 40%, despite therapy)
- Clinical Features
- • hallmark symptoms of decreased mental status and hypothermia; hyponatremia, hypotension, hypoglycemia, bradycardia, hypoventilation, and generalized edema often present
- Investigations
- • decreased T4, increased TSH, decreased glucose
- • ACTH and cortisol for evidence of adrenal insufficiency

Myxedema coma - treatment

- • Aggressive treatment required; ABCs: ICU admission
- • corticosteroids (for risk of concomitant adrenal insufficiency): Methylprednisolone 20 mg i.v. 4 times daily
- • Levothyroxine 0.2-0.5 mg IV loading dose, then 0.1 mg IV OD until oral therapy tolerated;
- • supportive measures: mechanical ventilation, vasopressor drugs, passive rewarming, IV dextrose,
- Fluids if necessary (risk of overload)
- • monitor for arrhythmia

Myxedema Coma (our experience)

Leading symptoms	Treatment	Common measures
Hypoventilation Hypercapnia Bradycardia Hypotension Pericardial effusion Absence of T-waves and low-voltage in ECG Hypo- to areflexia Constipation (to ileus) Hypothermia (up to 32˚C) Hyponatriemia (hemodilution) Inclination for hypoglycemia	First day: 500 g L-Thyroxin i.v. From 2nd day: 100 g L-Thyroxin i.v. for 1-2 weeks After that: transition to oral treatment Bulgaria: oral only 300-500 µg 1-2 days Then - 100 µg daily	Intubation, ventilation, bronchial toilet, stabilization of circulation, protection against heat loss (but not active warming!) because of danger of vasodilatation and hemodynamic collapse); application of Urbason 40-80 mg daily in the beginning for prophylaxis of possible adrenal insufficiency

Prognosis: pessimistic (up to 50% mortality despite treatment)

Subclinical hypothyroidism – Etiology

TSH mildly elevated, fT4-normal

- Most often – autoimmune disease (Hashimoto)
- Prior hyperthyroidism, treated with ATD, surgery or radioiodine
- Moderate or severe iodine deficiency
- Goitrogenic factors, birth defects etc.

Consequences of subclinical hypothyroidism

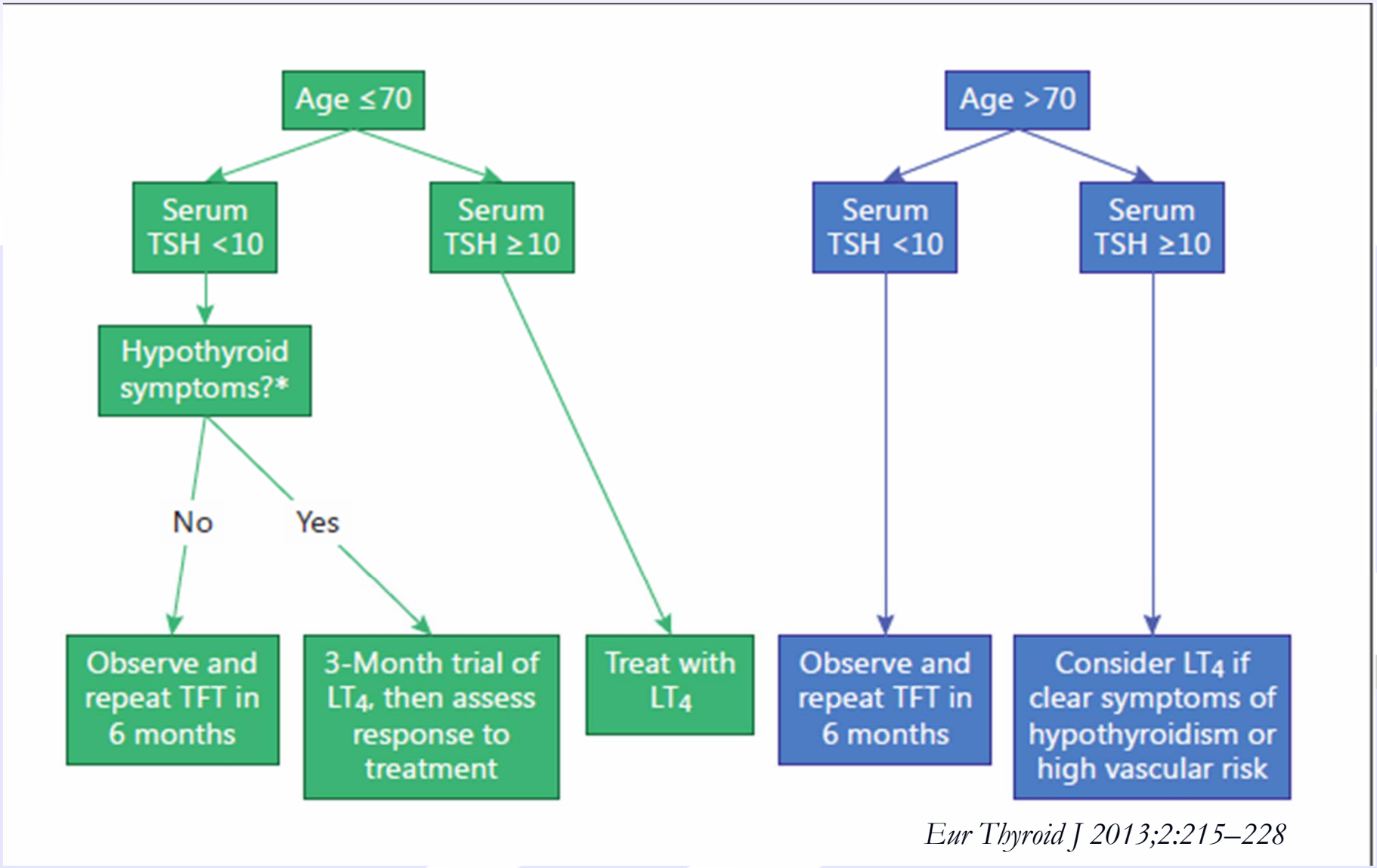
- **Lipid metabolism**: LDL↑↑, HDL↓, Tg↑
- **Cardiac function**:

Systolic intervals↓, contractility ↓,

atherosclerosis ↑↑

- **hematopoiesis**: Iron deficient anemia or Iron deficiency
- **Muscles**: dysfunction
- **Mental state**: Depression
- Main consequence – **mildly increased CV-events and mortality, especially if TSH > 7.0 and age < 65 yrs**

Clinical recommendations



Eur Thyroid J 2013;2:215–228

Non-toxic (simple) goiter

- Definition: generalized enlargement of the thyroid gland in a euthyroid individual that does not result from inflammatory or neoplastic processes
- Etiology
- • iodine deficiency or excess
- • goitrogens: brassica vegetables (e.g. turnip, cassava)
- • drugs: iodine, lithium, para-aminosalicylic acid
- • disorder of hormone synthesis with compensatory growth
- • peripheral resistance to thyroid hormone

Non-toxic (simple) goiter

- Pathophysiology
- • the appearance of a goiter is more likely during adolescence, pregnancy, and lactation because of increased thyroid hormone requirements
- ■ early stages: goiter is usually diffuse
- ■ later stages: multinodular non-toxic goiter with nodule, cyst formation and areas of ischemia, hemorrhage, and fibrosis

- Treatment
- • remove goitrogens
- • surgery preferred; necessary if severe compressive symptoms
- •radioiodine therapy (need very high doses, used as last resort)

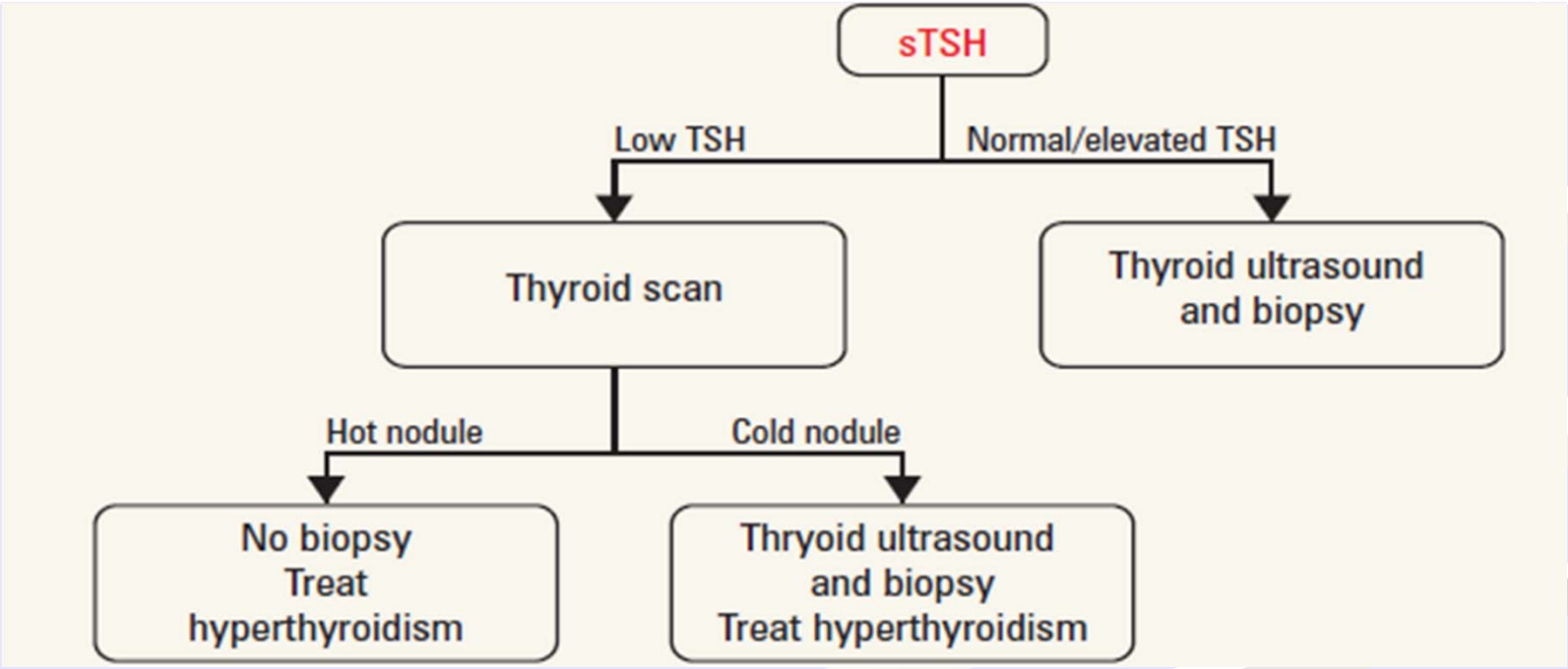
Non-toxic (simple) goiter

- Complications
- • compression of neck structures causing stridor, dysphagia, pain, and hoarseness
- • compression of neck structures causing stridor, dysphagia, pain, and hoarseness
- • multinodular goitre may become autonomous leading to toxic multinodular goitre and hyperthyroidism

Thyroid nodules

- Definition: clearly defined discrete mass, separated from the thyroid parenchyma
- • palpable nodules are found in approximately 5% of women and 1% of men; On US – in 15% of men and 30% of women (in Bulgaria)
- Etiology
- • benign tumors (e.g. colloid nodule, follicular adenoma)
- • hyperplastic area in a multinodular goitre
- • cysts: true thyroid cyst, area of cystic degeneration in a multinodular goitre
- • thyroid malignancy

Thyroid nodules – diagnostic approach



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Thyroid carcinoma

Approach to Thyroid Nodule

- all patients with thyroid nodules require evaluation of serum TSH and ultrasound
- intermediate-high suspicion nodule >1 cm and low suspicion nodule >1.5 cm should undergo FNA
- nodules <1 cm with clinical symptoms or lymphadenopathy may require further evaluation
- when performing repeat FNA on initially non-diagnostic nodules, U/S-guided FNA should be employed
- nuclear scanning has minimal value in the investigation of the thyroid nodule

FNA-biopsy is performed to assess thyroid cells and to exclude malignancy (accuracy ≈ 95%)
The cytologic diagnosis is based on the Bethesda Classification v. 2017

Table 18. Bethesda Classification of Thyroid Cytology

Category		Risk of Malignancy
Non-diagnostic or unsatisfactory	B I	Unknown
Benign	B II	0-3%
Follicular lesion of undetermined significance/ Atypia of undetermined significance	B III	5-15%
Follicular/hürthle cell neoplasms	B IV	15-30%
Suspicious for malignancy	B V	60-75%
Malignant	B VI	97-99%

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Thyroid carcinoma – an overview

Etiology	Epidemiology	Risk Factors
Thyroid (90% benign – 10% malignant)		
>80% papillary 5-15% follicular 5% medullary <5% anaplastic 1-5% hürthle cell 1-2% metastatic	Children Adults <30 or >60 yr Nodules more common in females Malignancy more common in males	Radiation exposure Family history – papillary CA or multiple endocrine neoplasia – MEN II Older age Male Papillary – Gardner's, Cowden's, familial adenomatous polyposis (FAP)
Parathyroid	Mean age: 44-55 yr Rare tumour	

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Thyroid carcinoma – an overview

	Papillary	Follicular	Medullary	Anaplastic
Incidence (% of all thyroid cancers)	70-80%	10-15%	1 to 2% (90% sporadic, 10% familial – test for RET germline mutation)	<2%
Route of Spread	Lymphatic	Hematogenous	Lymphatic and hematogenous	
Histology	Orphan Annie nuclei Psammoma bodies Papillary architecture	Capsular/vascular invasion Invasion influences prognosis	Amyloid May secrete calcitonin, prostaglandins, ACTH, serotonin, kallikrein, or bradykinin	Giant cells Spindle cells
Other	**P**s – **P**apillary cancer **P**opular (most common) **P**alpable lymph nodes **P**ositive I^{131} uptake **P**ositive prognosis **P**ost-operative I^{131} scan to guide treatments	**F**s – **F**ollicular cancer **F**ar away mets **F**emale (3:1) **F**NA (cannot be diagnosed by **F**NA) **F**avourable prognosis	**M**s – **M**edullary cancer **M**ultiple endocrine neoplasia (MEN IIa or IIb) a**M**yloid **M**edian node dissection	More common in elderly 70% in women 20-30% have Hx of differentiated thyroid Ca (mostly papillary) or nodular goitre mass Rapidly enlarging neck Rule out lymphoma
Prognosis	98% at 10 yr	92% at 10 yr	50% at 10 yr 20% at 10 yr if detected when clinically palpable	20-35% at 1 yr 13% at 10 yr
Treatment	Small tumours: Near total thyroidectomy or lobectomy Diffuse/bilateral: Total thyroidectomy ± neck dissection ± post-operative I^{131} treatment	Small tumours: Near total thyroidectomy/lobectomy/isthmectomy Large/diffuse tumours: Total thyroidectomy	Total thyroidectomy Median and/or lateral compartment node neck dissection (based on serum calcitonin) Modified neck dissection Post-operative thyroxine, radiotherapy Tracheostomy Screen relatives	Radiation and chemotherapy Small tumours: Total thyroidectomy ± external beam

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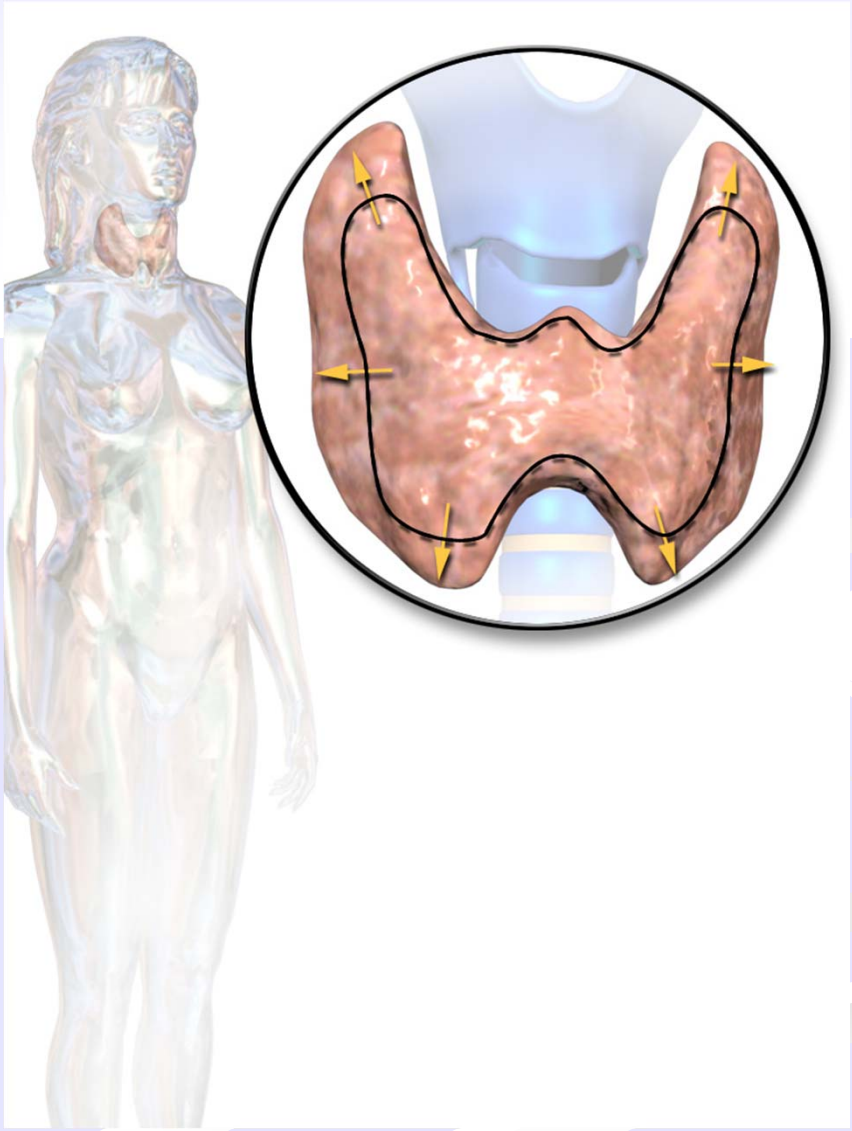
Thyroid carcinoma – clinical summary

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Clinical Features	Investigations	Treatment	Prognosis
Thyroid			
Thyroid mass, cervical nodes Vocal cord paralysis Hyper/hypothyroidism Dysphagia	FNA U/S	1° surgery I^{131} for intermediate and high risk well differentiated thyroid cancer	Recurrences occur within 5 yr Need long-term follow-up: clinical exam, thyroglobulin

Treatment	Indications
Radioiodine therapy	For the treatment of hyperthyroidism or as adjuvant treatment after surgery in the treatment of intermediate-high risk papillary or follicular carcinoma
Chemotherapy and/or radiotherapy	Recurrent/residual Medullary CA, Anaplastic CA or thyroid lymphoma
Surgical excision	Nodule that is suspicious on FNA cytology Malignancy other than anaplastic CA or thyroid lymphoma Mass that on FNA is benign but increasing in size on serial imaging and/or >3-4 cm in size Hyperthyroidism not amenable to medical therapy

Q and A



Suggested reading

2018 European Thyroid Association Guideline for the Management of Graves' Hyperthyroidism

George J. Kahaly[a] Luigi Bartalena[b] Lazlo Hegedüs[c] Laurence Leenhardt[d]
Kris Poppe[e] Simon H. Pearce[f]

Eur Thyroid J 2018;7:167–186

The 2015 European Thyroid Association Guidelines on Diagnosis and Treatment of Endogenous Subclinical Hyperthyroidism

Bernadette Biondi[a] Luigi Bartalena[b] David S. Cooper[c] Laszlo Hegedüs[d]
Peter Laurberg[e] George J. Kahaly[f]

Eur Thyroid J 2015;4:149–163

2016 American Thyroid Association Guidelines for Diagnosis and Management of Hyperthyroidism and Other Causes of Thyrotoxicosis

Douglas S. Ross,[1*] Henry B. Burch,[2**] David S. Cooper,[3] M. Carol Greenlee,[4] Peter Laurberg,[5†]
Ana Luiza Maia,[6] Scott A. Rivkees,[7] Mary Samuels,[8] Julie Ann Sosa,[9]
Marius N. Stan,[10] and Martin A. Walter[11]

DOI: 10.1089/thy.2016.0229

Suggested reading

2013 ETA Guideline: Management of Subclinical Hypothyroidism

Simon H.S. Pearce[a,b] Georg Brabant[c] Leonidas H. Duntas[d] Fabio Monzani[e]
Robin P. Peeters[f] Salman Razvi[a,g] Jean-Louis Wemeau[h]

Eur Thyroid J 2013;2:215–228

Guidelines for the Treatment of Hypothyroidism

Prepared by the American Thyroid Association
Task Force on Thyroid Hormone Replacement

Jacqueline Jonklaas,[1*†] Antonio C. Bianco,[2*‡] Andrew J. Bauer,[3†] Kenneth D. Burman,[4†]
Anne R. Cappola,[5†] Francesco S. Celi,[6‡] David S. Cooper,[7†] Brian W. Kim,[2‡] Robin P. Peeters,[8‡]
M. Sara Rosenthal,[9†] and Anna M. Sawka[10†]

DOI: 10.1089/thy.2014.0028

The 2016 European Thyroid Association/European Group on Graves' Orbitopathy Guidelines for the Management of Graves' Orbitopathy

Luigi Bartalena[a] Lelio Baldeschi[b] Kostas Boboridis[c] Anja Eckstein[d] George J. Kahaly[e]
Claudio Marcocci[f] Petros Perros[g] Mario Salvi[h] Wilmar M. Wiersinga[i]
on behalf of the European Group on Graves' Orbitopathy (EUGOGO)

Eur Thyroid J 2016;5:9–26

Suggested reading

2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer

The American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer

DOI: 10.1089/thy.2015.0020

European Thyroid Association Guidelines for Ultrasound Malignancy Risk Stratification of Thyroid Nodules in Adults: The EU-TIRADS

Gilles Russ[a] Steen J. Bonnema[b] Murat Faik Erdogan[c] Cosimo Durante[d] Rose Ngu[e] Laurence Leenhardt[a]

Eur Thyroid J 2017;6:225–237

2018 European Thyroid Association (ETA) Guidelines on the Diagnosis and Management of Central Hypothyroidism

Luca Persani[a, b] Georg Brabant[c] Mehul Dattani[d] Marco Bonomi[a, b] Ulla Feldt-Rasmussen[e] Eric Fliers[f] Annette Gruters[g, h] Dominique Maiter[i] Nadia Schoenmakers[j] A.S. Paul van Trotsenburg[k]

Eur Thyroid J 2018;7:225–237

The Bulgarian Thyroid Guideline

http://endo-bg.com/dobri-praktiki/

