

Hypothyroidism

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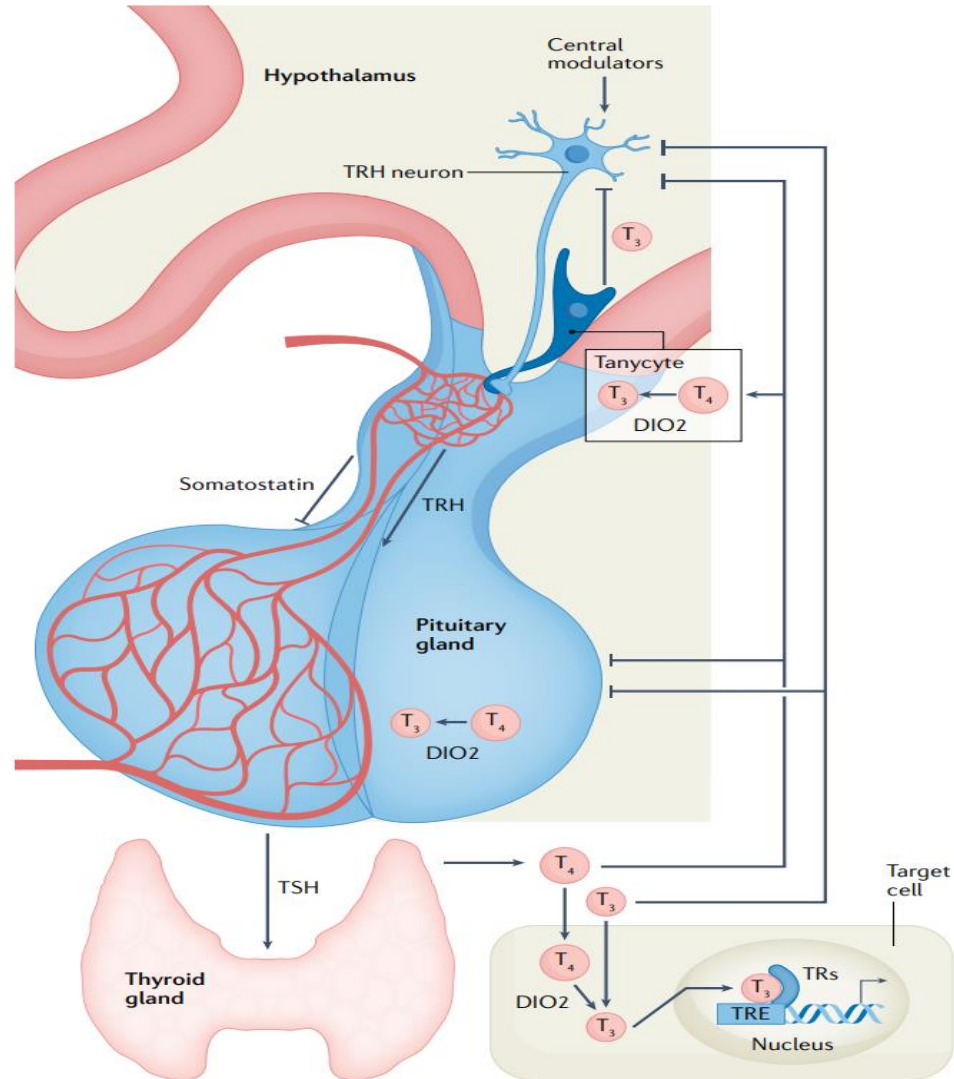
Case-1

- خانم ۳۳ ساله ای به علت افزایش وزن ۳ کیلوگرم، اولیگومنوره، ضعف و کرامپ های عضلانی مراجعه کرده است، و به علت $CPK=950$ به شما ارجاع داده شده است،
■ در بررسی آزمایشگاهی :
- $FPG=92$ $Cr=1$ $TSH=65$ $T_4=1$ $T_3RU=20\%$
- تشخیص؟

Agenda

- Physiology
- Epidemiology of hypothyroidism
- Etiology and pathogenesis of hypothyroidism
- Diagnosis of hypothyroidism
- Treatment of hypothyroidism
 - Type of treatment
 - Starting dose
 - Maintenance dose
 - Duration of treatment
 - Goal of treatment
 - Follow up
- Hypothyroidism in pregnancy

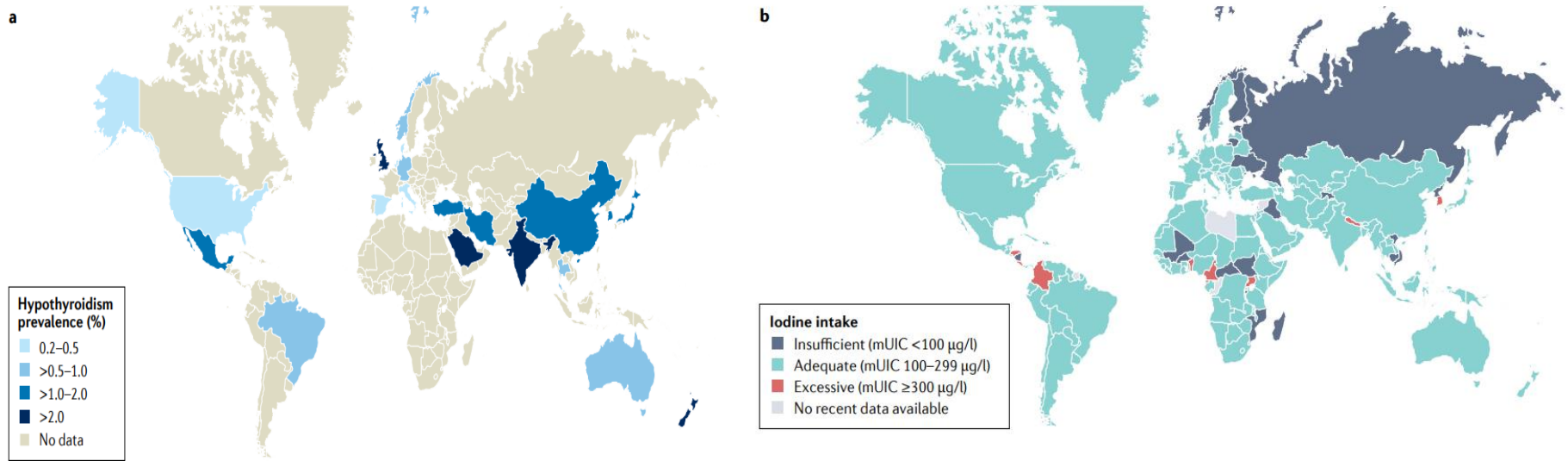
Regulation of thyroid function



Effects of Thyroid Hormone

- Fetal brain and skeletal maturation
- Increase in basal metabolic rate
- Inotropic and chronotropic effects on heart
- Increases sensitivity to catecholamines
- Stimulates gut motility
- Increase bone turnover
- Increase in serum glucose, decrease in serum cholesterol

Epidemiology



Prevalence of hypothyroidism (both overt and subclinical) : 4.6%

Overt hypothyroidism : 0.4%

*Subclinical hypothyroidism: 9% to over 20% among women >75 years
the risk of primary hypothyroidism is up to tenfold higher in women than in men*

Primary hypothyroidism prevalence is highest in populations with high iodine intake or severe iodine deficiency as compared with populations with a sufficient iodine status

Types of hypothyroidism

- *Primary Hypothyroidism:*
 - Congenital
 - Acquired
- *Secondary (central) Hypothyroidism:*
 - Congenital
 - Acquired
- *Peripheral Hypothyroidism:*
 - Congenital
 - Acquired

Etiology (types of Hypothyroidism)

Aetiology	Mechanism/pathophysiology
Primary hypothyroidism (thyroid)	
Chronic autoimmune thyroiditis (Hashimoto thyroiditis)	Failure of T cell-mediated inflammatory response, cytokine release, infiltration of the thyroid by lymphocytes and development of fibrotic tissue in the thyroid
Disturbed iodine metabolism	Iodine deficiency leads to decreased thyroid hormone production
	Iodine excess leads to thyroid hypofunction in patients with underlying primary thyroid disease
Irradiation and/or thyroidectomy	Ablation of thyroid cells
Genetic disease	Loss of function, pathogenetic variants
Infiltrative diseases and lymphoma	Infiltration of various cells or materials, granuloma and fibrosis formation, and thyroid cell destruction
Infection and/or inflammation	Thyroid cell destruction (most recently COVID-19 infection)
Medications ^a	Lithium: increased intrathyroid iodine content, decreased coupling of iodotyrosine and hormone release
	IFN α and IL-2: possible activation of autoimmune process
	Tyrosine kinase inhibitors: multiple mechanisms described, including effects on thyroid hormone metabolism and transport, and destructive thyroiditis
	Immune-checkpoint inhibitors: immune-related adverse events, including primary hypothyroidism, sometimes preceded by thyroiditis
Industrial and environmental agents	Interference in various steps of intrathyroidal metabolism

Etiology (types of Hypothyroidism)

Central hypothyroidism (hypothalamic or pituitary)

Pituitary or hypothalamic lesions and/or damage	Heterogeneous mechanisms leading to altered secretion of TSH by thyrotrophs and/or bioactivity of TSH, involving both hypothalamic and pituitary structures, usually combined with other pituitary hormone deficiencies, including surgery, head trauma, neoplastic lesions, apoplexy, pituitary necrosis, (partial) empty sella, infiltrative lesions or irradiations
Infection and/or inflammation	Infectious (for example, tuberculosis) or inflammatory (for example, sarcoidosis) causes leading to pituitary or hypothalamic infiltration or hypophysitis (for example, due to immune-checkpoint inhibitors)
Congenital	Midline defects, Rathke pouch cyst or genetic mutation; congenital genetic mutations rarely cause isolated central hypothyroidism but are more often part of combined pituitary hormone deficiencies and the most common defective genes are <i>PROP1</i> and <i>POU1F1</i>

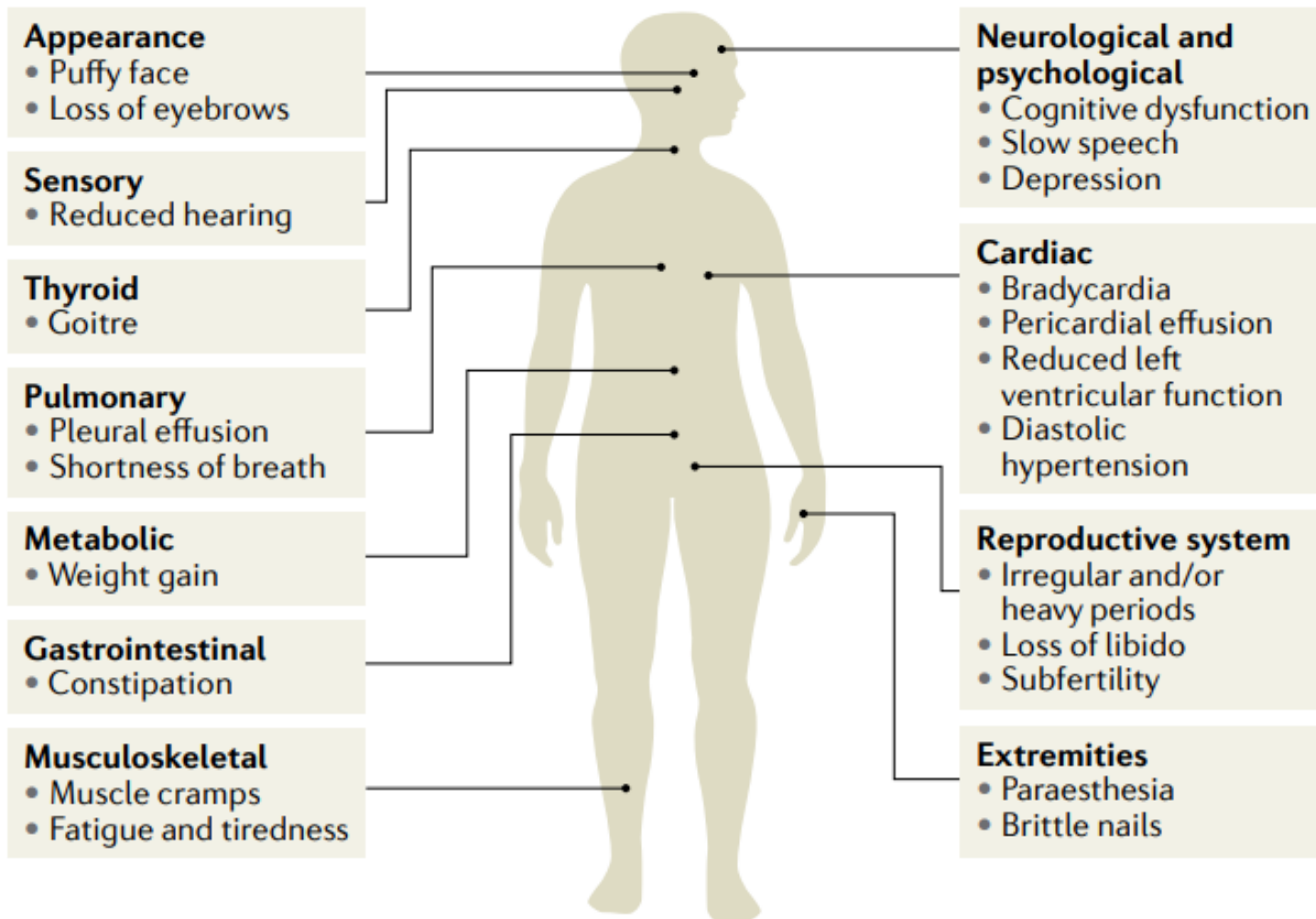
Peripheral hypothyroidism (peripheral tissues)

Consumptive hypothyroidism	Increased expression of type 3 iodothyronine deiodinase (for example, by tumour cells)
Resistance to thyroid hormone	Tissue-specific hypothyroidism owing to decreased sensitivity to thyroid hormone (resulting from mutations in, for example, <i>MCT8</i> , <i>THRA</i> or <i>THRB</i>)

Primary hypothyroidism

- Precipitating Factors:
 - *Genetic*
 - *Environmental factors:*
 - **Smoking:**
 - TPO antibody are lower in smokers than in non-smokers
 - TSH levels:
 - Lower in current smokers than in former smokers
 - Lower in former smokers than in never smokers
 - **Obesity:** associated with higher serum TSH levels
 - **Vitamin D and Selenium deficiency**
 - **Moderate alcohol intake**

Clinical Presentation



Differential diagnosis:

Box 1 | Differential diagnoses of hypothyroidism based on similar presenting symptoms

Endocrine conditions

- Addison disease: may present with increased thyroid-stimulating hormone levels that normalize after glucocorticoid replacement is commenced
- Obesity (particularly if associated with obstructive sleep apnoea)
- Menopause
- Hypopituitarism
- Type 1 diabetes mellitus
- Hypercalcaemia

Autoimmune conditions

- Coeliac disease
- Pernicious anaemia
- Rheumatoid arthritis

Chronic end organ damage conditions

- Chronic kidney disease

- Chronic liver disease
- Chronic heart failure

Haematological conditions

- Iron deficiency anaemia
- Multiple myeloma

Nutritional deficiencies

- Vitamin B₁, B₁₂ or D deficiency
- Folate deficiency

Mental health conditions

- Depression
- Anxiety
- Chronic stress
- Poor sleep pattern

Others

- Chronic fatigue syndrome
- Fibromyalgia
- Post-viral syndromes
- Dementia

Diagnosis:

■ *Serum TSH :*

- The most reliable marker for assessing thyroid status in most patients

- Pituitary disease is excluded and
- Patients are not on medications that alter TSH

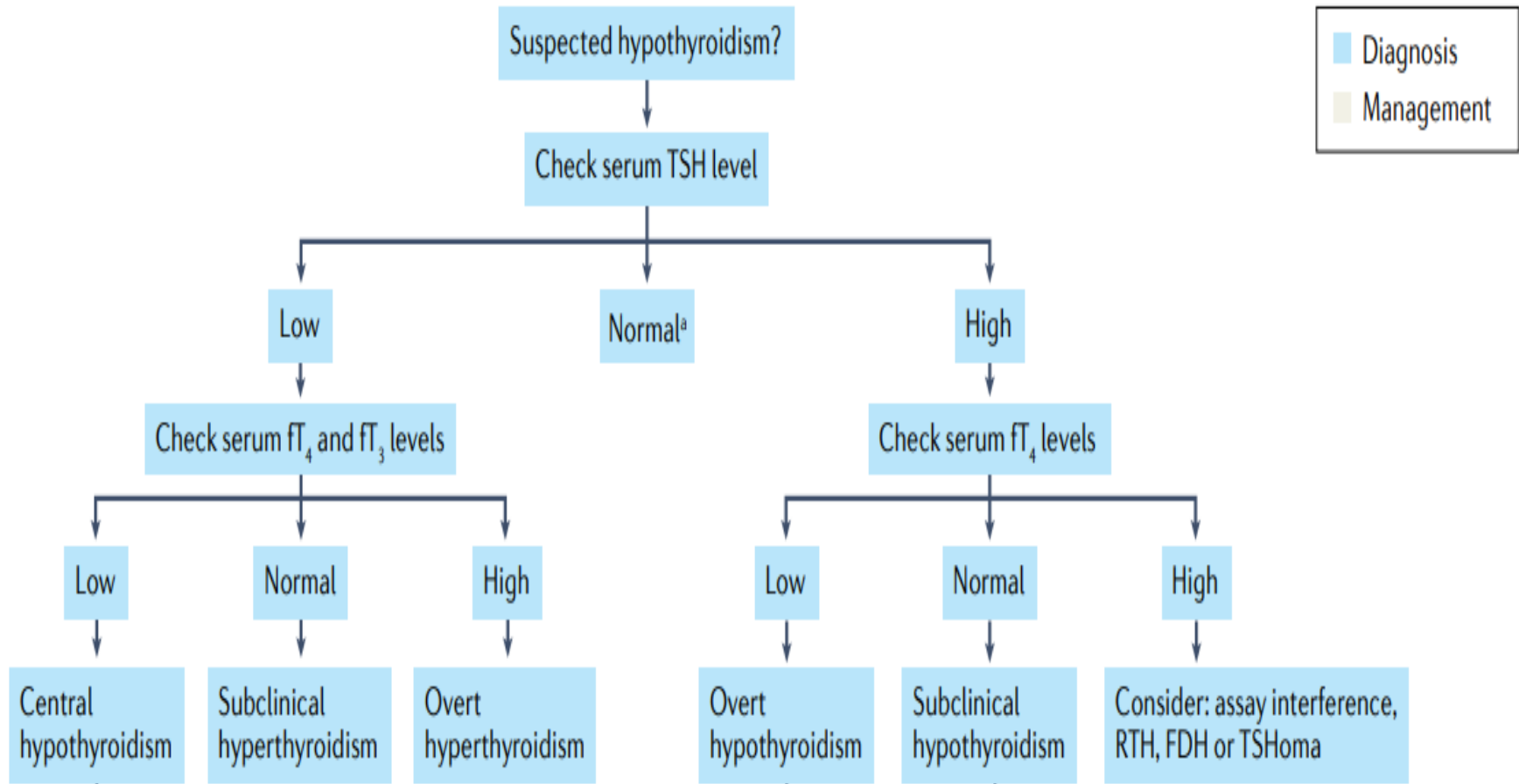
■ *log-linear relationship* between TSH and T4:

- Twofold decrease in fT4 levels is associated with a 100-fold increase in circulating TSH

Diagnosis:

- Measuring *markers of thyroid autoimmunity* (TPOAb or anti-tg antibodies) or *ultrasonography* (diffusely hypoechogenic, heterogeneous pattern) *are not required to diagnose hypothyroidism.*
- May be useful to confirm autoimmunity as the underlying cause

Diagnosis of Hypothyroidism:



Case -2

■ آقای ۷۲ ساله ای به علت پیوست ، ضعف و خستگی و افزایش وزن ۲ کیلوگرم در طی چند ماه اخیر مراجعه کرده است، در بررسی سابقه بیمار HTN و IHD داشته و ۱ سال قبل تحت جراحی CABG قرار گرفته است. در معاینه صورت پف آلود داشته و فاز برگشتی رفلکس آشیل تاخیری میباشد، تیروئید حدود ۳۵ گرم و با قوام firm میباشد. در بررسی آزمایشگاهی :

■ $TSH=35\text{mIU/l}$ $fT_4=3.5\mu\text{g/dl}$

■ تشخیص؟

■ درمان؟

■ روش مونیتورینگ؟

Thyroid hormone preparations

- Synthetic L-T₄
- Synthetic L-T₃
- Combined T₄ & T₃

Pharmacokinetics of oral thyroid hormones

	T ₄	T ₃
Absorption	~ 80%	~90%
Time to peak level	2-4 h	1-2h
Increase in serum concentration	20-40%	250-600%
Half-life	6-7days	~1days

Treatment :

- ***LT4 therapy*** is the mainstay of treatment for hypothyroidism
 - Should be taken consistently, ideally **60 min before breakfast**
 - taking LT4 30 min before breakfast or at bedtime on an empty stomach is also acceptable
- ***Typical full replacement doses:***
 - ***Adults:*** 1.6 µg/kg/day
 - Lower starting doses (25-50µg/day):
 - Older individuals
 - Those with mild hypothyroidism
 - Those with untreated cardiovascular disease
 - ***Infants:*** 10–15 µg/kg/day
 - ***Children:***
 - 1–3 years of age: 4–6µg/kg/day
 - 3–10 years of age: 3–5µg/kg/day
 - 10–16 years of age :2–4µg/kg/day

Medications that alter thyroid hormone absorption, binding or metabolism

Medications	Mechanism	Effect on LT4 requirements
Calcium carbonate, calcium citrate or calcium acetate; ferrous sulfate; proton-pump inhibitors; aluminium hydroxide; sucralfate; raloxifene; bile acid sequestrants	Decreased LT4 absorption	Increased (if LT4 doses not taken 4 h apart)
Phenytoin; phenobarbital; carbamazepine; rifampin; tyrosine kinase inhibitors	Increased thyroid hormone metabolism	Increased
Bile acid sequestrants	Reduced enterohepatic thyroid hormone circulation	Increased
Oral oestrogens; selective oestrogen receptor modulators; mitotane; opiates; 5-fluorouracil	Increased thyroxine-binding globulin levels	Increased
Androgens; nicotinic acid; chronic glucocorticoid therapy; danazol; L-asparaginase	Decreased thyroxine-binding globulin levels	Decreased
Amiodarone	Inhibition of 5'-deiodination (inhibits production of T ₃ from T ₄)	Increased

Malabsorption :

- Malabsorption of LT4 might occur following :
 - Bariatric surgery
 - Gastrointestinal disorders
- In patients with malabsorption, treatment with *liquid rather than tablet* LT4 formulations might help to stabilize TSH levels

Monitoring of treatment:

- **Primary Hypothyroidism:**

- **Serum TSH** should be monitored :
 - **6 weeks after** initiation of treatment or any change in dose
 - Then **every 6–12 months** thereafter.
- **Goal of treatment:** serum TSH in low reference range

- **Central Hypothyroidism:**

- **Serum fT4 level** in the upper half of the reference range

Monitoring of treatment:

- Thyroid hormone under-replacement and over-replacement should be avoided.
- Complication of over or under treatment:
 - *Cardiac :*
 - Cardiac arrhythmia
 - Progressive heart failure
 - *Bone:*
 - increased bone turnover leading to osteoporosis
 - *Catabolic muscle loss*
 - *Impaired quality of life*
 - *Increased mortality*

Case-3

- خانم ۲۸ ساله ای جهت بررسی قبل از اقدام به بارداری مراجعه کرده است ، در بررسی انجام شده :
- $fT_4=7.6$ $TSH= 6.9$ $TPOAb=250$
- تشخیص بیمار چیست؟
- بهترین اقدام شما چیست؟

Subclinical Hypothyroidism:

- The risk for progression from *subclinical* to *overt hypothyroidism* is **~2–4% annually** (more likely with positive TPOAb)
- Thyroid function ***should be retested after 8–12 weeks*** to determine whether the TSH elevation is persistent.
- **30–50%** of individuals who had high serum TSH levels ***have normal levels on retesting***

Subclinical Hypothyroidism:

- *Treatment Indications:*
 - Patients, especially those ≤ 70 years of age:
 - Have symptoms potentially referable to hypothyroidism
 - Cardiovascular risk factors
 - Goiter
 - Positive TPOAb
 - Planning pregnancy
 - Serum TSH level persistently >10 mIU/l

Case 4:

- خانم ۲۷ ساله در هفته هفتم بارداری با نتایج آزمایشات تیروئید به شما مراجعه کرده است، سابقه بیماری دیگری ندارد و به جز قرص یدوفولیک داروی دیگری مصرف نمی کند. سابقه هیپوتیروئیدی در مادر و دو خواهر بیمار مثبت است. در معاینه تیروئید دو برابر نرمال با قوام firm دارد. آزمایشات همراه بیمار:
 - $T_4=8.56$, $T_3ru=0.9$ TBI, $TSH=7.2$
 - اقدام بعدی شما؟

Hypothyroidism in pregnancy:

- The developing fetus relies entirely on maternal TH during critical phases of early brain development (before GA 16–20wks).
- In pregnancy:
 - Serum TBG levels are markedly increased
 - Thyroid hormone is rapidly metabolized by placental DIO₃

Hypothyroidism in pregnancy:

- ***Gestational hypothyroidism caused by :***
 - Iodine deficiency
 - untreated or undiagnosed overt hypothyroidism during pregnancy
- ***Adequate intake of iodine is important in:***
 - those with underlying autoimmune thyroid disease as iodine deficiency may trigger or worsen hypothyroidism.
- ***The recommended daily dose of iodine :***
 - 90 µg for pre-school children
 - 120 µg for school children
 - 150 µg in adults
 - 250 µg in pregnancy¹

Hypothyroidism in pregnancy:

- Complication of untreated overt hypothyroidism in pregnancy :
 - Miscarriage
 - Preterm delivery
 - Gestational hypertension
 - Pre-eclampsia
 - Low birthweight
 - Fetal death
 - Impaired child intellectual development.

Hypothyroidism in pregnancy:

- In women of childbearing age, *targeted case-finding for thyroid dysfunction* should be considered in :
 - Pregnant women from areas of moderate to severe iodine deficiency
 - Women with symptoms potentially attributable to thyroid dysfunction
 - Those with a personal and/or family history of thyroid disease
 - Women with recurrent miscarriage or unexplained infertility

Hypothyroidism in pregnancy:

- Most pregnant women on LT4 therapy will require an increase in LT4 dosing (25–30% as soon as pregnancy is diagnosed) to maintain euthyroidism during gestation.
- *Serum TSH levels* should be closely monitored, approximately *every 4 weeks* during the *first half* of gestation
- In pregnancy and the pre-conception period, LT4 dosing should target a serum TSH level of $<2.5\text{mIU/l}$

Hypothyroidism in pregnancy:

- Maternal subclinical hypothyroidism has been reported in ~4% of all pregnancies and has been suggested to be adversely related to pregnancy outcomes and child development

Hypothyroidism in pregnancy:

- LT4 treatment started before conception improves *assisted reproductive technology (ART)* outcomes when the baseline TSH level is $>4.0\text{mIU/l}$, particularly in women who are positive for TPOAb
- The recommended TSH target level in treated women is $<2.5\text{mIU/l}$
- It is not known whether pre-conception treatment of subclinical hypothyroidism improves fertility or pregnancy outcomes in women who conceive without assisted reproduction

Clinical guidelines for LT₄ treatment of thyroid disease in pregnancy

Organization (year of recommendations)	Subclinical hypothyroidism	Isolated maternal hypothyroxinaemia
American College of Obstetrics and Gynecology (2020)	Do not treat	Not discussed
American Thyroid Association (2017)	Treat if TSH level >10 mIU/l or if positive for TPOAb Consider treating if TSH level >4 mIU/l without TPOAb positivity	Do not treat
American Society for Reproductive Medicine (2015)	Treat with LT ₄	Not discussed
European Thyroid Association (2014)	Treat with LT ₄	Consider LT ₄ treatment if isolated hypothyroxinaemia is detected in the first trimester

Case-4

- خانم ۳۲ ساله ای با سابقه هیپوتیروئیدی تحت درمان با لووتیروکسین یک قرص روزانه به علت مثبت شدن تست بارداری جهت مشاوره مراجعه کرده است، در بررسی آزمایشات ۲ ماه قبل به شرح زیر بوده است:
 - $TSH=1.5$ $T_4=9.8$ $T_3RU=33\%$
- اقدام بعدی شما چیست؟

- نوع درمان؟
- دوز درمانی؟
- روش مونیٲورینگ؟
- نوع آزمایش؟
- زمان انجام آزمایش؟

Case-7

- آقای ۴۵ ساله ای به علت سردرد ضعف و خستگی از حدود ۴ ماه قبل مراجعه کرده است، در معاینه پوست خشک و صورت خشن دارد. در بررسی آزمایشگاهی :
- $TSH=5$ $T_4=2$ $T_3RU=20\%$
- اقدام بعدی شما کدام است؟

Take home message

- *Secondary hypothyroidism* is usually diagnosed in the context of other anterior pituitary hormone deficiencies.
- In secondary hypothyroidism TSH levels may be low, normal, or even slightly increased; the latter is due to secretion of immunoactive but bioinactive forms of TSH.



- The diagnosis is confirmed by detecting a low unbound T_4 level.
- The goal of treatment is to maintain T_4 levels in the upper half of the reference range, because TSH levels cannot be used to monitor therapy.

Case -8

- خانم ۳۶ ساله ای به علت اولیگومنوره ، سردرد و گالاکتوره مراجعه کرده است، در بررسی آزمایشگاهی :
 - $TSH=45$ $T_4=2.5$ $T_3RU=15\%$
 - $Prolactin = 91 \text{ ng/ml}$
- در MRI انجام شده بزرگی هیپوفیز گزارش کرده است،
- بهترین اقدام شما کدام است؟

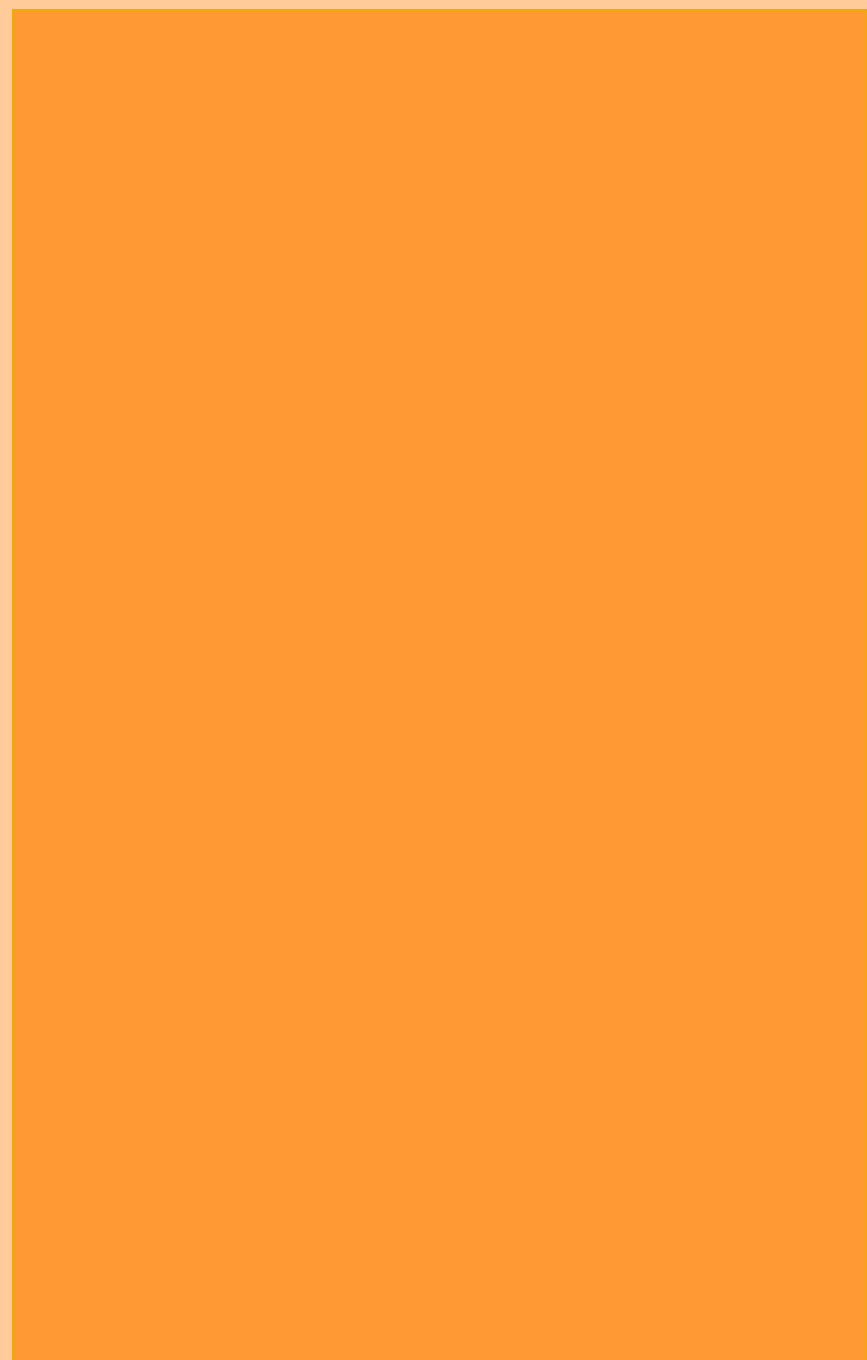
Indications to test for hypothyroidism†

Clinical symptoms and signs

Fatigue
Cold intolerance
Constipation
Impaired memory
Slowed mental processing
Depression
Nerve entrapment syndromes
Ataxia
Muscle weakness
Muscle cramps
Menstrual disturbance
Infertility
Bradycardia
Diastolic hypertension
Hoarseness
Goitre
Periorbital oedema
Weight gain
Galactorrhoea

Laboratory test abnormalities

Hypercholesterolaemia
Hyponatraemia
Hyperprolactinaemia
Hyperhomocysteinaemia
Anemia
Creatine phosphokinase elevation



Case-9

- آقای ۵۴ ساله ای به علت ضعف و تنگی نفس
فعالیتی مراجعه کرده است در معاینه HTN
دیاستولیک دارد در بررسی آزمایشگاهی :
- FPG=74 mg/dl total Cholesterol=307mg/dl
- TG=175 HDL=47 LDL=225 Cr=0.8
- U/A=NL AST=24 ALT=31
- اقدام بعدی شما چیست؟
- TSH=32 T₄=4 T₃RU=20%

Case-10

- خانم ۴۲ ساله ای با اختلال عادت ماهیانه به صورت هیپرمنوره مراجعه کرده است از گرفتگی عضلات پشت ساق پا و پarestزی دستها شاکی است، سابقه هیپرتیروئیدی حدود ۲ سال قبل داشته که به علت عدم پاسخ به درمان دارویی متی مازول و عود علائم ۵ ماه قبل ۲۰ میلی کوری ید ۱۳۱ دریافت کرده است.
- در بررسی آزمایشگاهی :
- $T_4=3$ $TSH=18$ $T_3RU=18\%$
- اقدام بعدی شما کدام است؟

- نوع درمان؟
- دوز درمانی؟
- روش مونیٲورینگ؟
- نوع آزمایش؟
- زمان انجام آزمایش؟
- مدت درمان؟

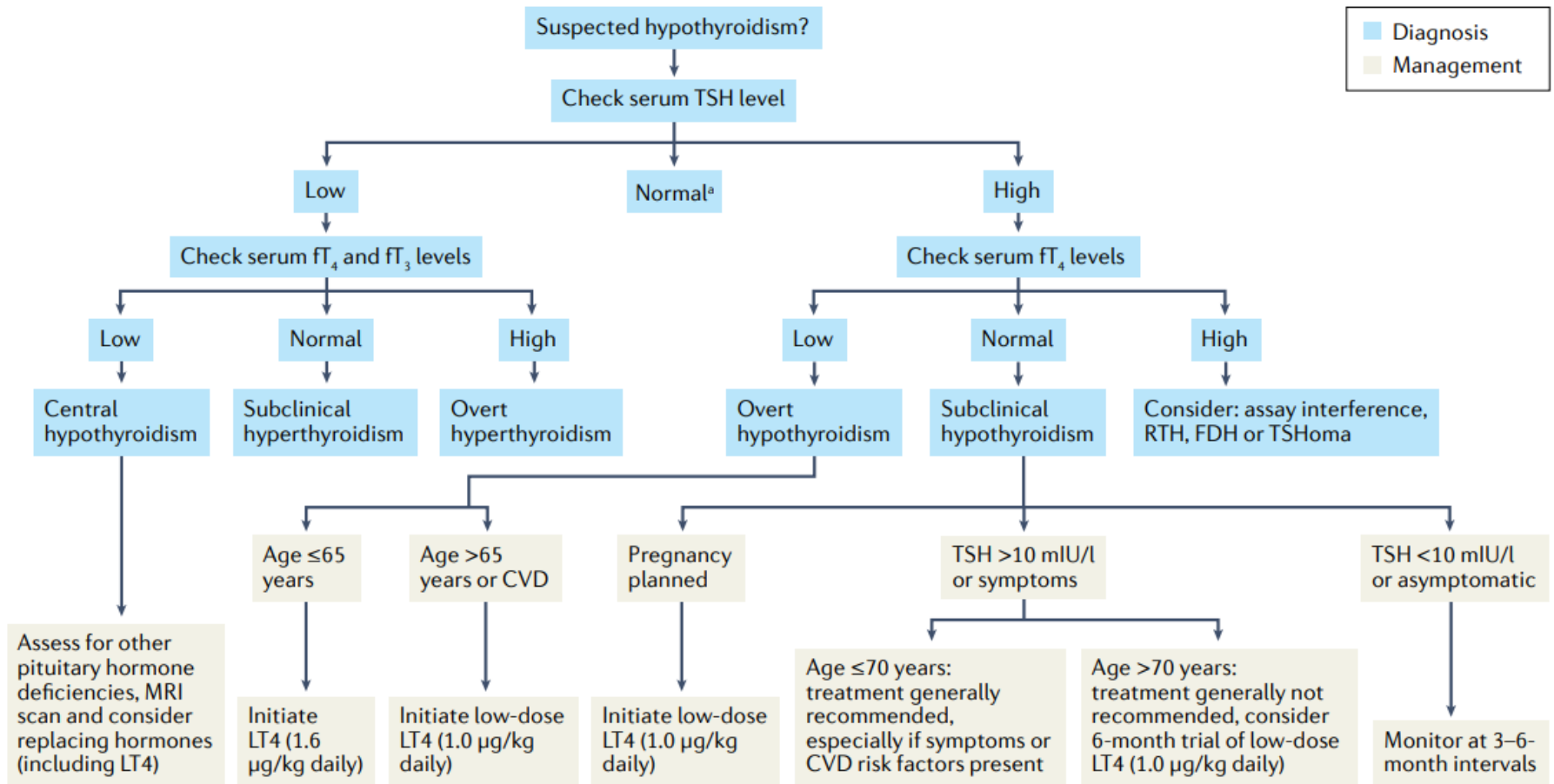
Case -11

- خانم ۶۳ ساله ای جهت مشاوره در مورد ادامه درمان به شما مراجعه کرده است، سابقه مصرف لووتیروکسین را از ۲۵ سال قبل به میزان یک قرص روزانه به صورت مرتب ذکر می کند و سابقه قطع داروی اخیر را در گذشته نمیدهد. در معاینه تیروئید سایز و قوام طبیعی دارد. در بررسی آزمایشات همراه :
 - $TSH=0.9$ $T_4=9.5$ $T_3RU=29\%$
 - بهترین اقدام برای بیمار کدام است؟

Duration of treatment:

- *Permanent Hypothyroidism:*
 - Life long
- *Transient Hypothyroidism:*
 - 6-12 months
 - Withdrawal of LT4 therapy after 6–12 months might be appropriate in these cases.

In summary:





Thanks For Your Attentions