"He who studies medicine without books sails an uncharted sea, but he who studies medicine without patients does not go to sea at all." – William Osler

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MEDICINE
TEAMWORK

THYROID DISORDERS

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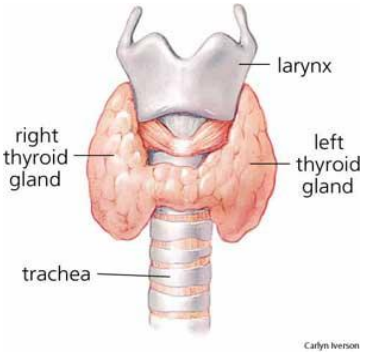
Thyroid Disorders

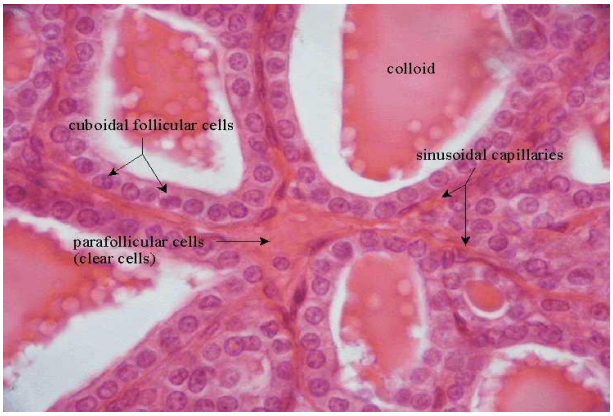
Thyroid Gland Anatomy:

- Thyroid gland is made up of follicles.
- Has 2 lobes and connected by the isthmus. (Butterfly shape)
- Weigh 20 g (you need to know the weight), more volume in men, increase with age and bodyweight and decrease with iodine intake. (The weight of the pituitary and thyroid glands increase with pregnancy)
- Located in front of larynx.

It is closely attached to the thyroid cartilage and to the upper end of the trachea, and thus moves on swallowing.



Thyroid Histology:



Colloid (iodinated glycoprotein) is synthesized by the Follicular cells. Parafollicular cells contain calcitonin-secreting C cells.

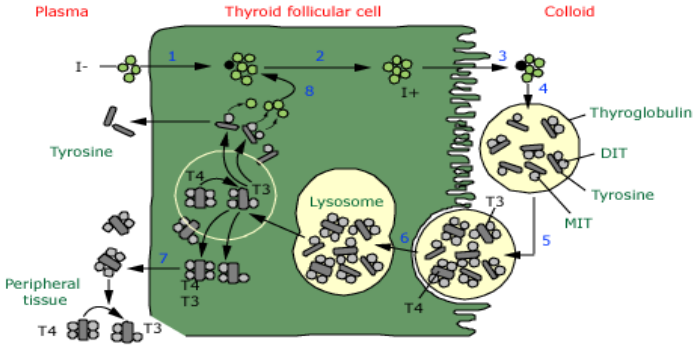
Thyroid Hormone (Function):

Thyroid hormones are: (difference between T3&T4 is the number of iodine molecules)

1- L-thyroxine(T4): is a prohormone.
2- Triiodothyronine(T3): acts at the cellular level

- Somatic development in adults.
- Brain development in infants.
- Fetal thyroid functions at 10-12 weeks of gestation.
- Maternal T4 reaches the fetus during development.(So it is very important to be corrected during pregnancy)
  - ✓ If the mother has hypothyroidism→ preterm delivery, miscarriage, cognitive impairment of infant.
  - ✓ (Also, Hyperthyroidism→ preterm delivery and miscarriage but NOT cognitive impairment of infant, it will advance the bone development and child will be short)
- Main action of thyroid hormones by T3: 80 % of T3 comes from the peripheral conversion and 20 % produced by the thyroid itself. (T4 produced by the gland and converted into T3 by the peripheral tissue)
- Follicular cells of the thyroid are the main site of hormones synthesis.
- Mainly T4 and small amount of T3.
- Iodine is needed to produce thyroid hormones.
- Average adult requirement of iodine is 150 mcg a day, 220 mcg for pregnant ladies, 290 mcg for lactating.
- Source of iodine: dairy and seafood products.

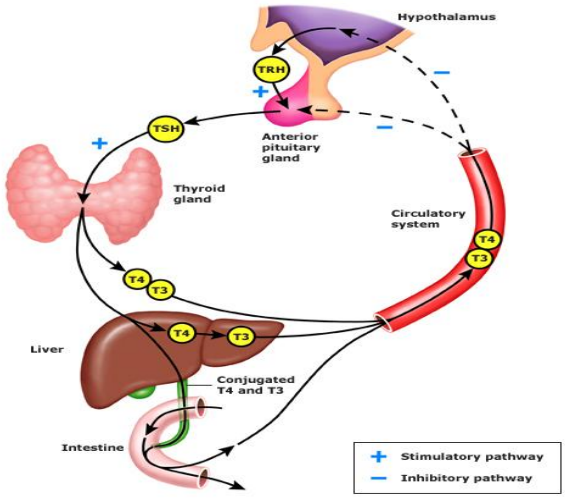
Thyroid hormones synthesis:-



In plasma thyroid hormones are mainly (more than 99%) bound to hormone binding protein [thyroxine –binding globulin TBG, thyroid-binding prealbumin TBPA and albumin]→ So, only Free T3&T4 (.1%) can be measured.

Thyroid Hormones

- Stored in the thyroglobulin in follicular cells of the thyroid gland.
- 99.9 % of T4 and T3 are bound to protein in the blood: TBG, albumin, lipoprotein.
- T4 and T3 synthesis and secretion is regulated by pituitary TSH.(Pituitary sense the need of thyroid hormones_ negative feedback_)
- TSH is inhibited by T4 and T3, stimulated by TRH.
- Extrathyroidal (peripheral) conversion of T4 to T3 is regulated by nutrition, illness (e.g. ICU patients), and hormonal factors.



Physical effects of thyroid hormones:

-CVS→ HR & CO.

-Skeletal→ ↑bone turnover & re-sorption.

-Respiratory→ maintains normal hypoxic & hypercapnic drive in respiratory center.

-GI→↑gut motility.

-Blood→↑RBS 2,3-BPG facilitating oxygen release to tissue.

-Neuromuscular→ ↑speeds of muscle contraction & relaxation & muscle protein turnover.

-Metabolism of carbohydrate→↑hepatic gluconeogenesis/glycolysis & intestinal glucose absorption.

-Metabolism of lipid→↑lipolysis & cholesterol synthesis &and degradation.

-Sympathetic nervous tissue→↑ catabolism sensitivity and β-adrenergic receptor numbers in heart, skeletal, adipose cells and lymphocytes + ↓ cardiac α- adrenergic receptors.

Thyroid hormone action:-

- Thyroid hormones act on the bone and bone development.
- In children: delayed growth and epiphyseal growth. (Deficiency)
- In brain: cognitive impairment. (Deficiency)
- Act on cardiac muscle: tachy and bradycardia.
- Regulate metabolic rate and little change in bodyweight.

Thyroid Function: (Assessment mainly by: TSH, FreeT3,FreeT4,and Thyroid Abs)

- TSH.
- Free T4, FreeT3.
- TRH. (Cant's measured in the blood only in the research lab)
- TBG.
- Thyroid antibodies: microsomal antibodies, TSH receptor antibodies, thyroglobulin antibodies. (There are specific Antibodies for the Hypo and Hyper–thyroidism)

Radiological imaging of thyroid function:

- US neck.
- Radioactive uptake scan.
- CT neck sometimes for retrosternal goiter. (CT is the best to evaluate retrosternal goiter)

Common thyroid disorders:

Goiter: (Surgery is done if it symptomatic)

- Goiter: chronic enlargement of thyroid gland not due to neoplasm.

Causes:

- Endemic Goiter: common in china and central africa. (iron deficiency areas)
- Sporadic Goiter: multinodular goiter.
- Familial.
- Hashimoto's thyroiditis: in early stage.
- Graves' disease: due to chronic stimulation of TSH receptor.
- Diet: Cabbage, Cauliflower.
- Chronic iodine excess (Excess or Deficiency in the iodine can cause goiter)
- Medication: lithium in 6%.
- Neoplasm.

Assess thyroid function by:

- Free T4, FT3
- TSH
- Ultrasound neck. (If is really big or retosternal→ CT)

Goiter-non Toxic [Treatment]:

- Thyroxine suprression therapy: not useful. (Doesn't affect the gland)
- Surgery:
  - If pressure symptoms.
  - Malignancy.
  - Lymphadenopathy.
- Radioactive iodine therapy.

Hyperthyroidism:

- Hypermetabolic state caused by increased availability of thyroid hormones.

Causes of hyperthyroidism

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)
Radiation thyroiditis
Palpation thyroiditis
Exogenous thyroid hormone intake
Excessive replacement therapy
Intentional suppressive therapy
Factitious hyperthyroidism
Ectopic hyperthyroidism
Struma ovarii
Metastatic follicular thyroid cancer

Major causes of hyperthyroidism according to the presence of a high or low radioiodine uptake. High uptake indicates increased new hormone synthesis by the thyroid whereas low uptake indicates release of preformed hormone, exogenous ingestion, or extrathyroidal hormone synthesis.

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*Graves's disease: [Hyperstimulation of the gland]

- Is the most common cause of hyperthyroidism.
- Serum IgG antibodies bind to TSH receptors in the tyhroid→ stimulation thyroid hormones production [they behave like TSH]. These TSH receptors Abs[TSHR-Abs] are specific for Grave's.

*Toxic adenoma(Solitary toxic nodule):

- The cause of 5% of hyperthysoidim.
- Doesn't usually remit after a coures of antithyroid drugs.

*Toxic multinodular goiter:

- Commonly in older women.
- Antithyroid drugs are rarely successful in inducing the remession,althoogh they can control the hypethyroidism.

*Hashitoxicosis:

- Intial toxic phase of Hashimoto's thyroiditis.
- -More common in women and most common in late middle age(Hashimoto's thyroiditis).

*Hyperemesis gravidarum: (In pregency)

- Escessive vomiting in the first trimeter due to high level of HCG (Humen Chronionic Gonadotrphing) which has the same structure of TSH→ stimulation of TSH receptors.
- It resolves by itsefl, no need for treatment

*Trophiblastic disease:

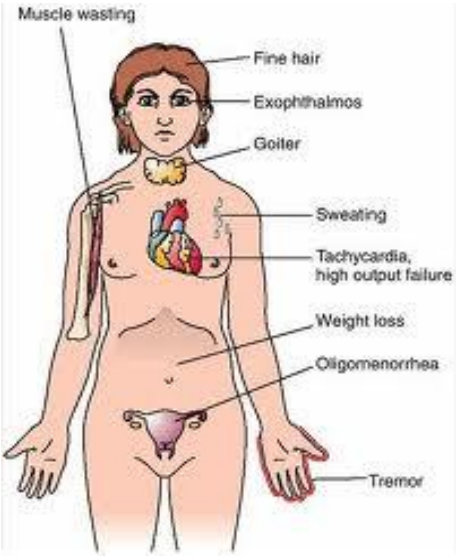
- In molar pregnency.
- Release a lot of HCG which is similar to TSH.

*Thyroiditis:

- Early stage of thyroid inflamation the is an increase in the thyroid hormones.

Clinical features of hyperthyroidism:

- Skin: warm, excessive sweating
- Onycholysis, hyperpigmentation
- Pruritus, vitiligo, alopecia, thining of the hair.
- (Grave's is an autoimmune disease that can afffect other autoimmune diseases such as : vitigo and alopecia)
- Pretibial myoxedema.
- Eyes: sympathetic overactivity.
- Common in graves' disease (Goiter+Eye symptoms→ Grave's)
- Extraocular muscles dysfunction: diplobia, proptosis, lid retraxtion, corneal ulceration, optic neuropathy (due to compression that results from the inflamation and infiltration of the extraocular muscle) and blindness.
- Periorbital and conjunctival odema
- Cardiac:
  - Atrial fibrillation in 10-20 %.
  - High output cardiac failure.
  - Wide pulse pressure, hypertension.
- Respiratory → Dyspnoea (Due to cardiac failure)
- GI: (High metabolic rate) → Weight loss, diarrhoea (increase frequency of bowl movement), increase liver enzyme.
- Bone → Bone turnover increased: osteoporosis
- Neuropsychiatry → Behavioral and personality changes: irritability, depression
- Hyperactivity increased and lack of concentration.
- Oligomenorrhea.



Lab-hyperthyroidism:

- Increased Free T4
- Increased Free T3
- Low TSH (Serum TSH is the initial test of choice)
- TSH-receptor antibodies (Specific for grave's, negative results only exclude Grave's as a cause of the hyperthyroidism)
- Increased radioactive iodine uptake on scan.

Treatment of Graves' hyperthyroidism

Therapy	Advantages	Disadvantages
Thionamides	Chance of permanent remission Some patients avoid permanent hypothyroidism Lower cost	Minor side effects: rash, hives, arthralgias, transient granulocytopenia, gastrointestinal symptoms Major side effects: agranulocytosis, vasculitis (lupus-like syndrome), hepatitis Risk of fetal goiter and hypothyroidism 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 Rare radiation thyroiditis Patient concerns about long-term oncogenic effects of radiation
Surgery	Rapid, permanent cure of hyperthyroidism	Permanent hypothyroidism Risk of hypoparathyroidism, recurrent laryngeal nerve damage, and general anesthesia High cost

Summary of the advantages and disadvantages of the three major therapeutic modalities used in the treatment

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-Surgery is the last choice unless there are obstructive symptoms.
-Radioiodine is more effective than antithyroid drugs because it has a permanent effect) (Medications have high recurrence rate).
-All the treatment modalities have hypothyroidism as side effect, so they need thyroxine.

Treatment:

- Beta blockers for immediate control of adrenergic symptoms
- PTU is preferred during pregnancy

Hypothyroidism:

Major causes of hypothyroidism

Primary hypothyroidism
Chronic autoimmune thyroiditis
Iatrogenic
Thyroidectomy
Radioiodine therapy or external irradiation
Iodine deficiency or excess
Drugs - thionamides, lithium, amiodarone, interferon-alfa, interleukin-2, perchlorate
Infiltrative diseases - fibrous thyroiditis, hemochromatosis, sarcoidosis
Transient hypothyroidism
Painless (silent, lymphocytic) thyroiditis
Subacute granulomatous thyroiditis
Postpartum thyroiditis
Subtotal thyroidectomy
Following radioiodine therapy for Graves' hyperthyroidism
Following withdrawal of suppressive doses of thyroid hormone in euthyroid patients
Congenital thyroid agenesis, dysgenesis, or defects in hormone synthesis
Central hypothyroidism
TSH deficiency
TRH deficiency
Generalized thyroid hormone resistance

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Drugs affecting thyroid function or function tests

Drugs causing hypothyroidism
Inhibition of thyroid hormone synthesis and/or release - thionamides, lithium, perchlorate, aminoglutethimide, thalidomide, and iodine and iodine-containing drugs including amiodarone, radiographic agents, expectorants (Organidin, Combid), kelp tablets, potassium iodine solutions (SSKI), Betadine douches, topical antiseptics
Decreased absorption of T4 - cholestyramine, colestipol, colesevelam, aluminum hydroxide, calcium carbonate, sucralfate, iron sulfate, raloxifene, omeprazole, lansoprazole, and possibly other medications that impair acid secretion, sevelemer, lanthanum carbonate, and chromium; malabsorption syndromes can also diminish T4 absorption
Immunedysregulation - interferon-alfa, interleukin-2
Suppression of TSH - dopamine
Possible destructive thyroiditis - sunitinib
Increased T4 clearance and suppression of TSH - bexarotene
Drugs causing hyperthyroidism
Stimulation of thyroid hormone synthesis and/or release - iodine, amiodarone
Immunedysregulation - interferon-alfa, interleukin-2, denileukin diftitox
Drugs causing abnormal thyroid function tests without thyroid dysfunction
Low serum TBG - androgens, danazol, glucocorticoids, slow-release niacin (nicotinic acid), l-asparaginase
High serum TBG - estrogens, tamoxifen, raloxifene, methadone, 5-fluouracil, clofibrate, heroin, mitotane
Decreased T4 binding to TBG - salicylates, salsalate, furosemide, heparin (via free fatty acids), certain NSAIDs
Increased T4 clearance - phenytoin, carbamazepine, rifampin, phenobarbital
Suppression of TSH secretion- dobutamine, glucocorticoids, octreotide
Impaired conversion of T4 to T3 - amiodarone, glucocorticoids, contrast agents for oral cholecystography (eg, iopanoic acid), propylthiouracil, propanolol, nadol

Major symptoms and signs of hypothyroidism

Mechanism	Symptoms	Signs
Slowing of metabolic processes	Fatigue and weakness Cold intolerance Dyspnea on exertion Weight gain Cognitive dysfunction Mental retardation (infant) Constipation Growth failure	Slow movement and slow speech Delayed relaxation of tendon reflexes Bradycardia Carotenemia
Accumulation of matrix substances	Dry skin Hoarseness Edema	Coarse skin Puffy facies and loss of eyebrows Periorbital edema Enlargement of the tongue
Other	Decreased hearing Myalgia and paresthesia Depression Menorrhagia Arthralgia Pubertal delay	Diastolic hypertension Pleural and pericardial effusions Ascites Galactorrhea

Hypothyroid-Diagnosis:

- High TSH (Most sensitive indicator of hypothyroidism)
- Low Free T4 and T3
- Positive TPO antibodies
- Low Na
- Anemia
- High cholesterol

Treatment:

- Thyroxine replacement.

Patterns of thyroid function tests during assessment of thyroid function

Serum TSH	Serum Free T4	Serum T3	Assessment
Normal hypothalamic-pituitary function			
Normal	Normal	Normal	Euthyroid
Normal	Normal or high	Normal or high	Euthyroid hyperthyroxinemia
Normal	Normal or low	Normal or low	Euthyroid hypothyroxinema
Normal	Low	Normal or high	Euthyroid: triiodothyronine therapy
Normal	Low normal or low	Normal or high	Euthyroid: thyroid extract therapy
High	Low	Normal or low	Primary hypothyroidism
High	Normal	Normal	Subclinical hypothyroidism
Low	High or normal	High	Hyperthyroidism
Low	Normal	Normal	Subclinical hyperthyroidism
Abnormal hypothalamic-pituitary function			
Normal or high	High	High	TSH-mediated hyperthyroidism
Normal or low*	Low or low-normal	Low or normal	Central hypothyroidism

* In central hypothyroidism, serum TSH may be low, normal or slightly high.

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Hypo and hyperthyroidism:

KNOW MORE

HYPOTHYROIDISM

It is a disease affecting humans and vertebrates, caused by insufficient production of thyroid hormones by the thyroid gland

- Poor muscle tone (muscle hypotonia)
- Fatigue
- Cold intolerance, greater sensitivity to cold
- Constipation
- Depression
- Muscle cramps and joint pain
- Goiter
- Thin, brittle fingernails
- Coarse hair
- Paleness
- Decreased sweating
- Poor muscle tone (muscle hypotonia)

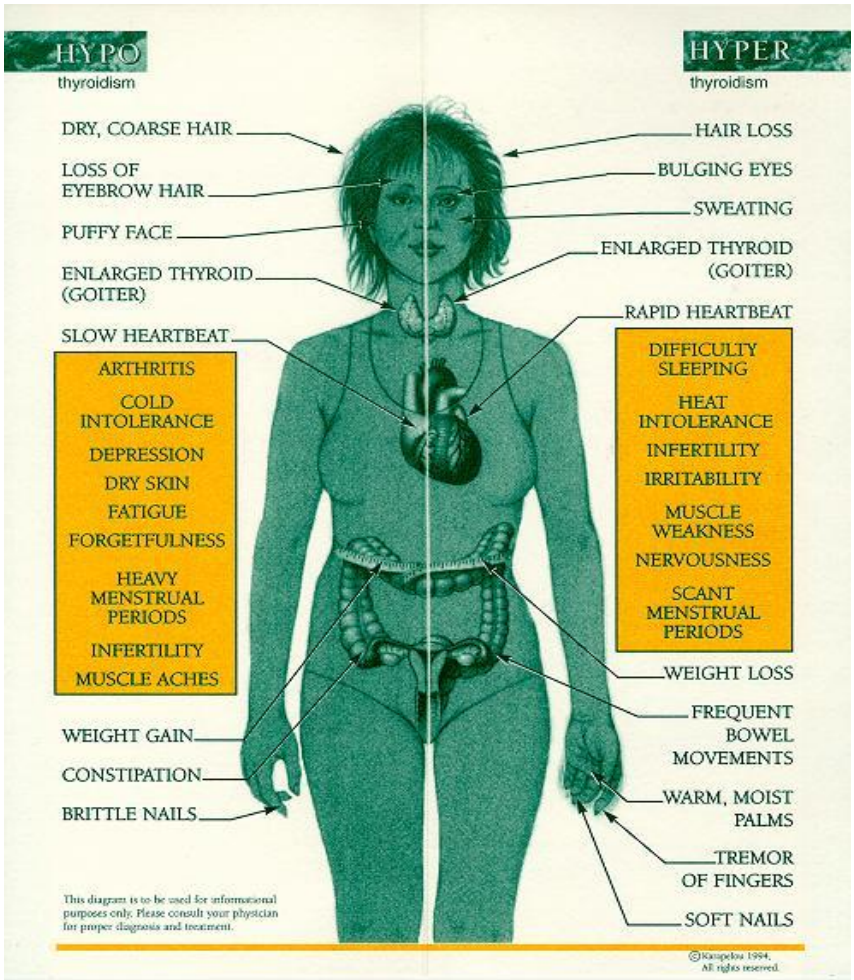
HYPERTHYROIDISM

It is a condition in which an overactive thyroid gland produces excessive amount of thyroid hormones that circulate in the blood

- Palpitation
- Heat intolerance
- Nervousness
- Insomnia
- Breathlessness
- Increased bowel movements
- Light or absent menstrual periods
- Fatigue
- Fast heart rate
- Trembling hands

Weight loss

- Muscle weakness
- Hair loss



MCQs

1. Most common cause of thyroiditis is ?
   a- hashimoto's thyroiditis
   b- reidl's thyroiditis
   c- subacute thyroiditis
   d- viral thyroiditis

2. In pregnancy ?
   a- thiouracil is contraindicated
   b- surgery is contraindicated
   c- radioiodine is contraindicated
   d- none

References:

- Kumar clinical medicine.
- Step-Up to Medicine