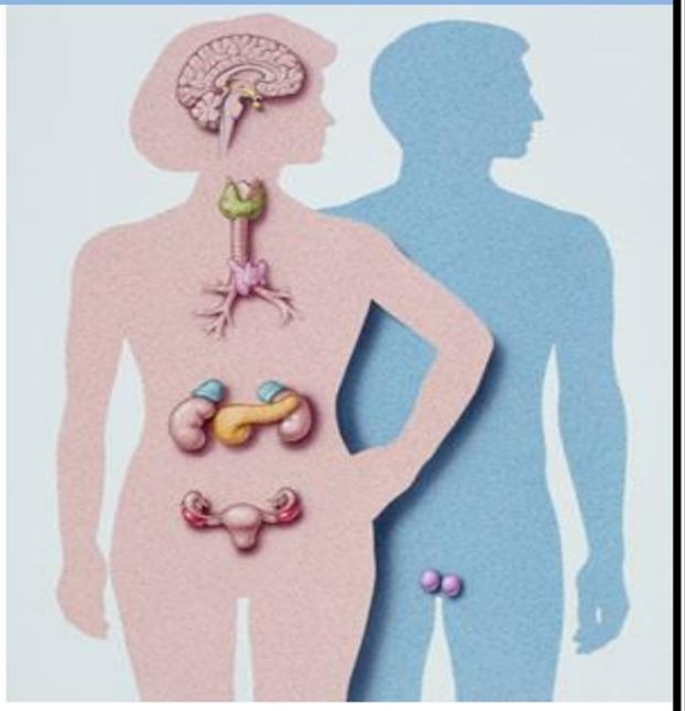
University of Jordan - Faculty of Medicine
(2013-19)

Medical Committee
The University of Jordan

Endocrine System



- ☐ Anatomy/Embryology/Histology
- ☐ Biochemistry
- ☐ Physiology
- ☐ Pharmacology
- ■ Pathology
- ☐ PBL

☐ Slide ■ Sheet ☐ Handout ☐ Other

Lecture #: **2** Date:

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Designed by: Zakaria W. Shkoukani

Thyroid gland

The thyroid gland is typically made of right and left lobes connected by an isthmus;the thyroid gland appears as clusters of cells forming follicles with **variable sizes.**

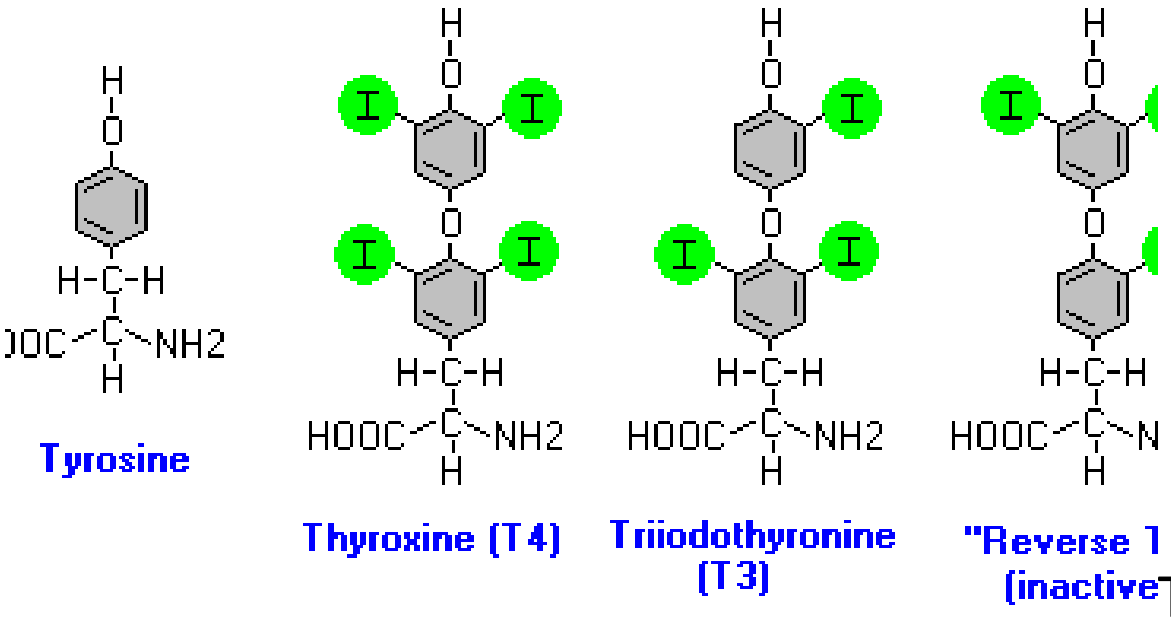
The follicular cells are cuboidal in shape, and they have basophilic nucleus. The follicles are lined with follicular cells and are filled with a fluid known as colloid that contains the prohormone thyroglobulin. The follicular cells contain the enzymesneeded to synthesize thyroglobulin

☒ Thyroid Hormone Synthesis

- ☒ The first step in the synthesis of thyroid hormones is the organification of iodine. Iodide is taken up, converted to iodine, and then condensed onto tyrosine residues which reside along the polypeptide backbone of a protein molecule called thyroglobulin. This reaction results in either a mono-iodinated tyrosine (MIT) or di-iodinated tyrosine (DIT) being incorporated into thyroglobulin. This newly formed iodothyroglobulin forms one of the most important constituents of the colloid material, present in the follicle of the thyroid unit.

- ☒ The other synthetic reaction, that is closely linked to organification, is a coupling reaction, where iodotyrosine molecules are coupled together. If two di-iodotyrosine molecules couple together, the result is the formation of thyroxin (T4). If a di-iodotyrosine and a mono-iodotyrosine are coupled together, the result is the formation of tri-iodothyronine (T3).In need these thyroglobulin are taken inside the cells under the effect of a process called pinocytosis. -

Thyroid hormones



- T3 and T4 ,the numbers (3and 4) refer to the number of iodine
- Iodine is an essential trace element; the thyroid hormones thyroxine and triiodothyronine contain iodine that's why iodine deficiency results in Hpothyroidism

☒ Para follicular cells are pale-staining cells found in small number in the thyroid which primary function is to secrete calcitonin

Regulators of Ca level in the blood:

✓ Many factors are involved in calcium homeostasis which include PTH, and Calcitonin

CalcitoninvsPTH

☒ Calcitonin

✓ It is a hormone that is produced in humans by the **parafollicular** cells (commonly known as **C-cells)** of the thyroid gland. Calcitonin is involved in helping to regulate levels of calcium and phosphate in the blood, **opposing** the action of parathyroid hormone

✓ It decreases plasma calcium levels, it takes the calcium into the bone.

☒ PTH: essentially acts to increase the concentration of calcium in the blood , it takes the calcium out of the bone

▪ Thyroid diseases

✓ Similar to endocrine diseases, thyroid diseases include both mass and hormonal diseases.

✓ The mass diseases involve inflammation (thyroiditis)and goiter (just means **enlargement** of the gland).

Note: Having a goiter doesn't necessarily mean that your thyroid gland isn't working normally. Even when it's enlarged, your thyroid may produce normal amounts of hormones. It might also, however, produce too much or too little thyroxine and T3 (**there is No relation**

between the above two. I.e. if there is a big mass, that doesn't mean that there will be an overproduction of the hormone)

- ✓ Through the hormones it produces, the thyroid gland influences almost all of the metabolic processes in your body. Thyroid disorders can range from a small, harmlessgoiter (enlarged gland) that needs no treatment to life-threatening cancer. The most common thyroid problems involve abnormal production of thyroid hormones. Too much thyroid hormone results in a condition known as hyperthyroidism. Insufficient hormone production leads to hypothyroidism.

- Thyroid diseases include:
  - ✓Hyerthyroidism
  - ✓Hypothyroidism
  - ✓Thyroiditis
  - ✓Graves disease
  - ✓Diffuse nontoxic goiter and multinodular goiter
  - ✓neoplasms

- Let us start with

THYROTOXICOSIS:

We should know the difference between thyrotoxicosis and hyperthyroidism (**important**)

- Hyperthyroidism: is the condition that occurs due to excessive **production** of thyroid hormone **by the thyroid gland.**

- Thyrotoxicosis:is the condition that occurs due to excessive thyroid hormone of **any cause** and therefore includes hyperthyroidism; it can be from thyroid or extra thyroidal tissue and it can be excessive **Release or Production**
  But clinically they are almost the same.

☒There are two types of thyrotoxicosis

A) Associated with hyperthyroidism (Thyroid hyper function):

1. ***Primary***

- The problem is in the thyroid itself***:***

✓ Diffuse toxic hyperplasia (Grave's disease)

Grave's disease is an immune system disorder that results in the thyroid **enlargement** (mass effect) and **increased production of thyroid hormones**

✓ Hyper functioning (Toxic) multinodular goiter

✓ Hyperfunctioning (toxic) adenoma

2) Secondary

✓ The problem is in the hypothalamus or pituitary glands

✓ TSH-secreting pituitary adenoma **(rare)**, it's rare because TSH pituitary adenomais only 1% of pituitary adenomas.

B) Thyrotoxicosis not associated with hyperthyroidism is less common

- ✓ Excessive **release (** not excessive production) of pre-formed hormone in **thyroiditis** (increase thyroid hormones in the blood)
- ✓ Ectopic secretion of thyroid hormones from extra thyroidal tissues.

Clinical manifestations of thyrotoxicosis

Too much thyroid hormones speed things up and too little thyroid hormones slow things down. They:

- Control the rate at which your body burns calories (your metabolism). This affects whether you gain or lose weight. They increase the metabolism
- They increase the destruction of lipids and production of proteins
- They stimulate the sympathetic effect
- Can slow down or speed up your heartbeat.
- Can raise or lower your body temperature.
- Change how fast food moves through your digestive tract.
- Affect muscle strength.

☒ Here's what you *may* experience:

A) Constitutionalsymptoms:

- ✓ *warm flushed* skin,
- ✓ heat intolerance and excessive sweating
- Both of them ,resulting from increasing the sympathetic stimulation

✓ Weight loss (due to increased lipid and carbs destruction)despite increased appetite.

B). Malabsorption, and diarrhea. (As a result of increased GI motility)

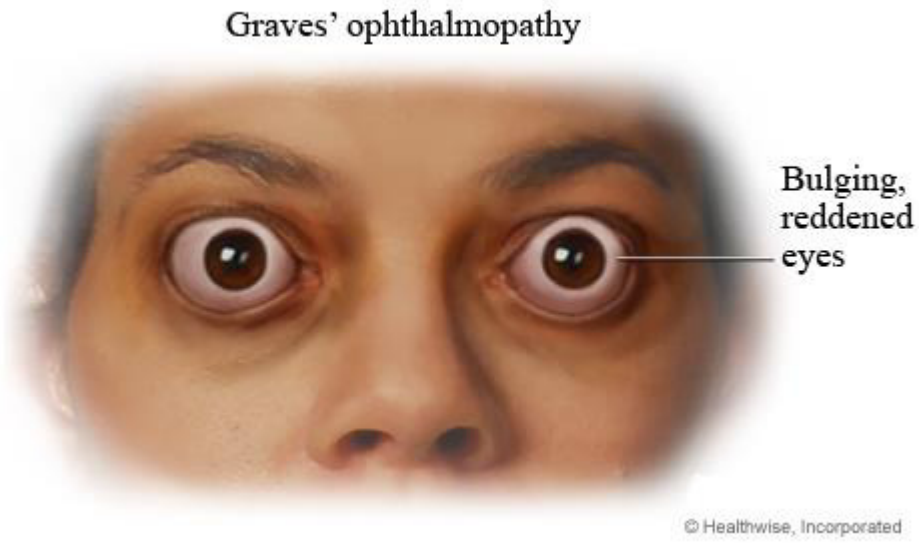
C). Tachycardia(heart rate that exceeds the normal resting rate), **Cardiac arrhythmia**, also known as **cardiac dysrhythmia** or **irregular heartbeat**, is a group of conditions in which the heartbeat is irregular; too fast, or too slow.Elderly patients may develop heart failure due to aggravation of pre-existing heart disease

☒ *D). N*ervousness, tremor, and irritability

E). A wide, staring gaze and lid lag because of sympathetic overstimulation of the levator palpebrae superioris

To stare: is to gaze with eyes wide open, as from surprise, wonder or alarm

- **Note**: you should distinguish between **wide, staring graze** and **ophthalmopathy**
- ✓ **Wide, staring gaze:it happens withany form of thyrotoxicosis of hyperthyroidism.**



- ✓ Ophthalmopathy: bulging, reddened eyes(the eyeball moves anteriorly)
- ✓ This problem happens only in **grave's disease**

☒Notes

☒ So ocular manifestation of Hyperthyroidism can be two things

- Wide staring gaze which occurs with any form of Thyrotoxicosis
- Ophthalmopathy which occurs only in Grave's disease

☒ True *thyroid ophthalmopathy* associated with proptosisis a feature seen only in Grave's disease.

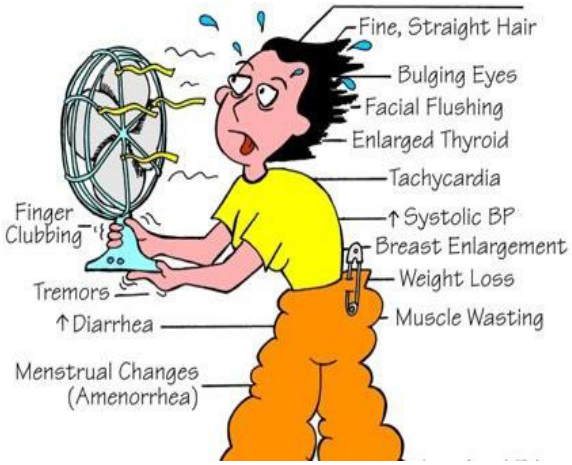
F). 50% develop proximal muscle weakness (*thyroid myopathy*).

G). Thyroid storm:

- ✓ Itis a rare but severe and potentially life-threatening complication of hyperthyroidism. It is characterized by a high fever, fast and often irregular heart beat
- ✓ It Designates the abrupt onset of severe hyperthyroidism(**sudden increase of thyroid hormones**), and this condition occurs most commonly in individuals with **Graves' disease**and it is a **medical emergency**because significant numbers of untreated patients (especially elderly patients) die of cardiac arrhythmias. It happens with any cause of thyrotoxicosis.Also, when we give the HYPOTHYROIDISM patients overdose of T3 and 4 ,thyroid storm will develop

  To sum up:

  Thyroid storm
  - Sudden increase of thyroid hormones
  - Most common with Graves ' disease
  - Medical emergency: because it affects the heart and leads to cardiac arrhythmia and tachycardia



Lab tests

- *The measurement of serum TSH is the most useful single screening test for hyperthyroidism,* because TSH levels are decreased (by negative feedback of T3 and T4) even at the earliest stages, when the disease may still be subclinical
- *TSH is always low in hyperthyroidism ,unless the primary disease is* ***Pituitary(adenoma)or Hypothalamus*** **disease**

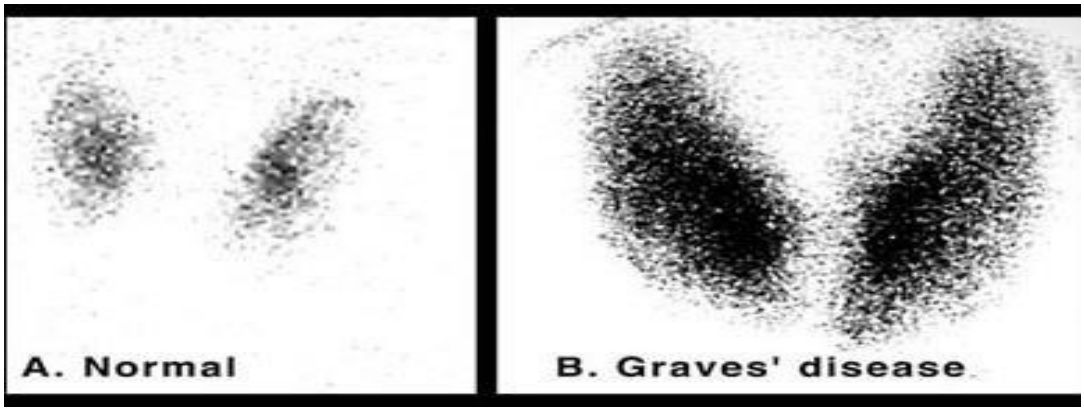
☒ Once the diagnosis of thyrotoxicosis has been confirmed measurement of radioactive iodine uptake by the thyroid gland often is valuable in determining the **etiology** (to see where the problem is; if the thyroid is taking iodine or not).

☒ Iodine is important in the production of thyroid hormones, so hyper- functioning thyroid takes more iodine than hypo-functioning thyroid.

☒ For example, such scans may show :

✓ a. Diffusely **increased (whole-gland)** uptake in Graves disease,

- ✓ b. **Increased** uptake in a **solitary** nodule in toxic adenoma
- ✓ C. **decreased** uptake in thyroiditis.



Note: Graves' disease is diffuse symmetrical bilateral enlargement

- ❖ There is two types of nodules are used to describe findings on a radioactive iodine uptake scan

- Cold nodule A thyroid nodule with a much **lower uptake** of radioactive iodine than t he

  Surrounding parenchyma; not taking iodine because they are not secreting thyroid hormone(hypo-functioning nodule)

- Hot nodule: A thyroid nodule with a much **higher uptake** of radioactive iodine, it is darker than the rest of the gland (Hyper – functioning nodule)

❖ HYPOTHYROIDISM :

- ✓ Is a common endocrine disorder in which the thyroid gland does not produce enough thyroid hormone

Primary causes: Thyroid disorder

a. - Worldwide, the most common cause of hypothyroidism is **dietary deficiency of iodine.**(Mainly in developing countries) and high mountains where iodine sources may be deficient

b. In most developed countries, autoimmune diseasespredominate such as**Hashimoto thyroiditis**

C. Genetic defects such as Thyroid *dysgenesis or*Congenital biosynthetic defect (dyshormogentic goiter)or defects in the enzymes that used in the production of thyroid hormones

- Conclusion: Primary causes are
- ✓ NO production of thyroid hormones, because there is iodine or enzymatic deficiency
- ✓ Production of auto- antibodies against the hormones

Secondary causes: **Pituitary or hypothalamic disorder**

2ND PART

This sheet is composed of 2 parts, hypothyroidism and thyroiditis(slides18-35)

It was written according to sec1&2 and some notes from Wikipedia

I've rearranged a lot of repeated information here and there so don't panic.

Hypothyroidism clinical manifestations,

We talked about the mechanism of hypothyroidism and how does it happen, now we'll talk about the clinical manifestations for hypothyroidism

• In children

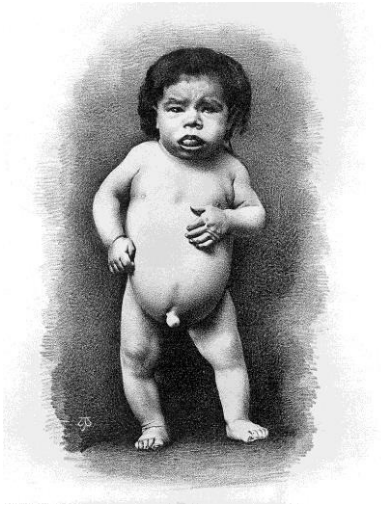
If it's seen in infancy and early childhood it's called Cretinism. If it presents in older children it's called myxedema. These cases are important because they are related to brain development, if hypothyroidism occurs while the brain is still developing (like in cretinism), mental retardation can be manifested. If it happens later in life, the brain would be normal but some other signs and symptoms may be present. That's why it's important to screen infants after birth for thyroid hormones to save these children from mental retardation. Physical growth can be affected as well and the child will exhibit dwarfism, as well as living a short life and being infertile.
Now we'll talk about them in more details.

♦Cretinism

Refers to hypothyroidism developing in infancy or early childhood. It can be:

1_endemic: it means 10% of the population have this disease, caused by dietary iodine deficiency

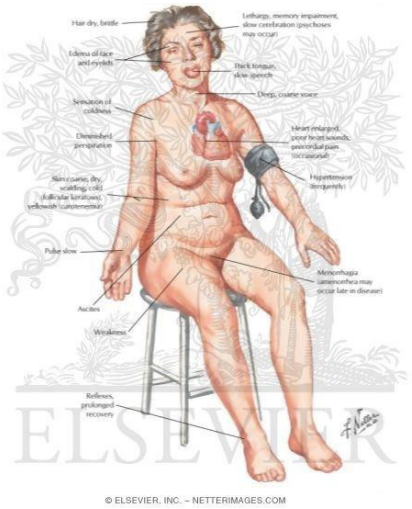
2_sporadic: Caused by enzyme defects that interferes with thyroid hormone synthesis



•Clinical features of cretinism includes (from slide):

- Impaired development of the skeletal system
- short stature(the most important)
- Coarse facial features, protruding tongue, umbilical hernia.
- Central nervous system, with mental retardation

♦Myxedema. or Gull syndrome



Hypothyroidism in older children and adults after the development of the brain has been achieved. (The doctor says she doesn't know why it's called myxedema, because this term is usually related to edema not of fluids but polysaccharides. Don't confuse it with tibial edema which happens in graves' disease.)

characterized by(from slides):

- Patients are cold intolerant, and often obese.
- Generalized apathy and mental sluggishness that in the early stages of disease may mimic depression
- Broadening and coarsening of facial features, enlargement of the tongue, and deepening of the voice.
- Bowel motility is decreased, resulting in constipation
- Pericardial effusions are common; in later stages, the heart is enlarged, and heart failure may supervene.
- Mucopolysaccharide-rich edematous fluid accumulates in skin, subcutaneous tissue, and number of visceral sites

Lab test shows an increase in TSH hormones because it doesn't have the normal negative feedback from thyroid hormones.

•Thyroiditis

We have many types of thyroiditis however the most common one is hashimoto thyroiditis. It's the leading cause of hypothyroidism in areas where iodine is sufficient. It's an autoimmune disease.

Having said that lets talk a little bit about autoimmune diseases and their mechanism. As we know the main cells of the immune system are b-cells and t-cells. T-cells recognize forging antigens, however they don't recognize our own antigens and they don't attack them, how? During development these cells recognize our antigens and all the clones of b and t cells that were made to attack these antigens get deleted. For some reason in autoimmune diseases -mainly genetic- some of these clones persist until maturation and they start to function again, making antibodies against our antigens. Another reason may be that sometimes those antigens have been hiding in human cells and locked away from the blood stream. Due to some kind of trauma, infection or any abnormality they get out and are recognized as foreign bodies by those stupid t and b cells, and an autoimmune reaction occurs. :/

•hashimoto thyroiditis

What happens here is that antibodies are produced against thyroid antigens, especially TSH-receptors, causing them to be blocked and stopping their function. The thyroid thus becomes unresponsive to TSH and gets destroyed.

Autoantibodies stimulate T-helper cells which in turn stimulate all other cells of the immune system: other t-helpers, cytotoxic t-cells and B cells.

[note: T-cells have 2 sub-types: t-helper(CD4) and cytotoxic t-cells(CD8)

(CD4,8 are certain receptors on the cell)]

All these cells cause destruction of the gland:

>t-helper destroys the cells by producing cytokines such as IFN-γ

>cytotoxic t-cells kill the cell directly (through FAS)

> b-cells can become plasma cells and produce immunoglobulins which cause destruction of the cells through antibody dependent cytotoxicity (mainly antibody production)

The net effect here is destruction of the follicular epithelial cells. This can lead the colloid to leak outside the follicles and the conversion to T3 and T4 causing hyperthyroidism (hashitoxicosis). Keep in mind that this is only the initial stage, but later on hypothyroidism will happen because of that destruction.

All autoimmune diseases in general have some genetic predisposition:
- Concordance of disease in 40% of monozygotic twins
- The presence of circulating anti-thyroid antibodies in 50% of asymptomatic siblings of affected patients.

Two important findings are important to diagnose hashimoto thyroiditis:

1- Lymphoid aggregates with germinal centers

Wiki-((**Germinal centers** (or **germinal centres**; **GC**) are sites within secondary lymphoid organs where mature B lymphocytes proliferate, differentiate, and mutate their antibody genes (through somatic hypermutation), and switch the class of their antibodies (for example from IgM to IgG) during a normal immune response to an infection. They develop dynamically after the activation of follicular (Fo) B cells by T-dependent antigen.))-wiki

2- Metaplastic epithelial cells. Less hormones require the cells to function more, thus changing their shape from cuboidal and increasing their size and organelles to form **Hürthle cells.** These Hurthle cells have numerous mitochondria and their cytoplasm appears eosinophilic because of that.

This is how it appears under the microscope slide29

Fibrosis could happen (important point) what makes it special? In hashimoto thyroiditis the fibrosis is confined to the gland.

ALWAYS if a patient came to you with an autoimmune disease expect other autoimmune diseases like lupus or arthritis, why? Because the same mechanism that is responsible for hashimoto disease can also be responsible for other autoimmune diseases.

Patients with hashimoto are at increased risk for the development of B cell non-Hodgkin lymphomas within the thyroid gland.

Can it increase the risk for thyroid carcinoma? It's debatable.

•Subacute Granulomatous (de Quervain)Thyroiditis

- Is much less common than Hashimoto disease. It is believed to be caused by a viral infection and a majority of patients have a history of an upper respiratory infection just before the onset of thyroiditis.

Grossly- The gland has intact capsule, and may be unilaterally or bilaterally enlarged.

Histologic examination reveals disruption of thyroid follicles, with extravasations of colloid causing granulomas thyroiditis. The thing is, after the viral attack, the follicles are disrupted and the colloid is expelled out, the extravasated colloid acts as a foreign material and provokes a granulomatous reaction with giant cells that contain fragments of colloid.

Clinical Features(from slide) **:**

- Acute onset characterized by ***neckpain*** (because it's an infection) with swallowing
- Fever, malaise, and variable enlargement of the thyroid.
- Transient hyperthyroidism may occur as a result of disruption of follicles and release of excessive hormones.
- The leukocyte count is increased.

- With progression of disease and gland destruction, a transient hypothyroid phase may ensue.
- The condition typically is self-limited, with most patients returning to a euthyroid state within 6 to 8 weeks

Healing occurs by resolution of inflammation and fibrosis.

•Subacute Lymphocytic Thyroiditis :

It could be an autoimmune disease but the actual mechanism is unknown. It's less common than the others. The main point is that we can see lymphoid aggregates. How can we differenciate between it and hashimoto? Hashimoto has Hürthle cells however subacute lymphocytes has lymphoid aggregates alone.

And in a subset of patients the onset of disease follows delivery (postpartum thyroiditis). If she has it after the first child, there is a risk that she might develop this condition again with the next children.

•Riedel thyroiditis:

A rare disorder of unknown etiology, some evidence shows that it could be an autoimmune disease. It's characterized by extensive ***fibrosis*** involving the thyroid and contiguous structures simulating a thyroid neoplasm because it's infiltrative and can fix the gland to the surrounding tissue, however it's benign.

If you see a female patient with a hard, immobile gland think of malignancy because usually benign conditions are represented with soft glands, with some exceptions and this one is an exception.

It can develop into malignant tumor but this is rare!

It may be associated with idiopathic fibrosis in other parts of the body, such as the retroperitoneum.

Good luck in your midterms. And a special thanks goes to Bilal Sibai for giving me his earphones.

True laughter comes only from despair-**Raja'i Zurikat**