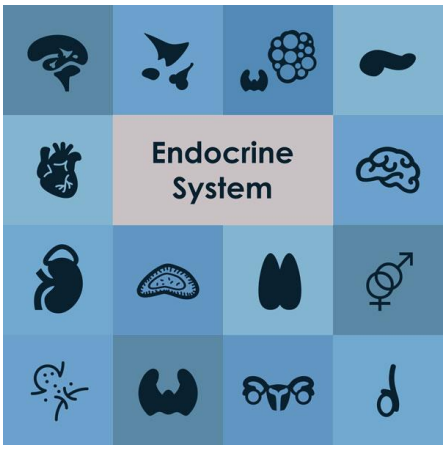
BAU-Medicine



Sheet no. 3
Lecture Date : 31/12/2020 (HAPPY NEW YEAR!)
Lecture Title : Diseases of thyroid & parathyroid glands 1 (continuation)
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دعاء لأخينا رشيد

اللهمَّ إن رشيد فِي ذِمَّتِك، وَ حَبْل جِوارِكَ، فَقِهِ منْ فِتنة الْقَبْرِ، وعذابِ النَّارِ، أنت أَهْلُ الْوفَاءِ والْحَق، فَاغْفِرْ لَهُ وَارْحَمْهُ إنَّكَ أنت الغَفورُ الرَّحِيمُ

Clinical scenarios

The thyroid function test (TFT) :
***We measure free T4 & free T3...these have feedback on TSH .**
***T3 is stronger than T4 in activating receptors…T4 is converted to T3 peripherally .**
***Minor change in T3/T4 will cause a large change in TSH level .**
***Most of the time we take free T4 & TSH and analyze their levels for the diagnosis .**

If we want to choose just one test, TSH is the best

- There is a laboratory test called **thyroid function test (TFT)** that measures free T4, free T3 and TSH .
- There's a **simple algorithm** depends on the increase/the decrease of these values (mainly free T4 and TSH) and it approaches us to the diagnosis of the issue in the patient .
- As we know, if free T4,free T3 increase, TSH decreases **(feedback inhibition)** and if T4,T3 decrease, TSH increases .
- T4 is converted to T3 **peripherally** **(T3 is a stronger activator** for the receptors in tissues) .
- A **slight** change in T3,T4 causes a **large** change in TSH **(TSH is more sensitive) .**
- **CENTRAL (secondary) :** the problem begins from the **pituitary** gland then affects the thyroid gland . (**both elevated or both decreased** = Central) : The patient should make pituitary MRI (if both elevated, it can be pituitary adenoma) .

- **NOT CENTRAL** : the problem begins from the **thyroid** gland then affects the pituitary gland (feedback) . (**one elevated and the other decreased** = Not central) .

Now let's begin with clinical scenarios :

- **Low T4 and high TSH = primary hypothyroidism**

  Thyroid gland releases **less T4** so pituitary gland releases **more TSH**

- **Low T4 and low TSH = central (secondary) hypothyroidism**

  Pituitary gland **doesn't release TSH** so thyroid gland **doesn't release T4** because thyroid gland is getting less TSH **(low TSH causes → low T4)**

- **High T4 and high TSH = central hyperthyroidism**

  Pituitary gland **releases more TSH** so thyroid gland **releases more T4** because thyroid gland is getting more TSH **(high TSH causes → high T4)**

- **High T4 and low TSH = Not central hyperthyroidism**

  Thyroid gland releases **more T4** so pituitary gland releases **less TSH**

  (Not necessarily primary) : Hyperthyroidism can be caused by a problem in the **thyroid itself (primary : more T4 → less TSH)** or by an **exogenous** factor (e.g. Drug; thyroxine : **more T4 from outside → less TSH**)

- **Normal T4 and high TSH = subclinical primary hypothyroidism**

  There's a problem in the thyroid gland that somehow **elevates TSH** but **T4 is normal** in blood (it's not clear)

- **Low T4 and normal or mildly elevated TSH = also central hypothyroidism**

> **TSH can't increase** in response to the **low T4** (problem in TSH secretion/problem in pituitary gland so the patient needs to have MRI)

- **Normal T4 and low TSH ⟶ check T3 (if high : T3 thyrotoxicosis) ,(if T3 is not high : subclinical hyperthyroidism)**

> **-Decrease in TSH, but T4 is normal** and **T3 is normal : (subclinical primary hyperthyroidism) .**
> **-Decrease in TSH, but T4 is normal** and **T3 is high : (T3 thyrotoxicosis) .**

- **High T4 and normal or mildly decreased TSH = also central hyperthyroidism**

> **TSH can't decrease** in response to the **high T4** (the patient needs MRI)

Approach to thyrotoxicosis patient (how to reach a diagnosis) :

> The examples and scenarios mentioned here are not the whole examples but they are enough at this level

***If** blood result shows high TSH and high T4 ⟶ **central hyperthyroidism :** Do **pituitary MRI (most appropriate next step) .**

***If** **non-central hyperthyroidism :** Do **uptake,** which is a special radioactive test that uses iodine as a tracer **(most appropriate next step) .**

…if the **uptake is high**, the next step is to do **scan** (to see the anatomical distribution of the uptake) it may be :

1/ Graves (in scan : **homogenous**=the whole thyroid gland is over-uptaking the radioactive material homogenously and diffusely) .

2/ Toxic adenoma (in scan : **1 spot**) .

3/ Toxic multinodular goiter (in scan : **multiple spots**) .

…if the **uptake is low**, next step is to measure **thyroglobulin** :

1/ if it is **high**: **thyroiditis** (because thyroglobulin increases in the blood with thyroid cell destruction).

Although we have high T3 and high T4 in blood and hyperthyroidism (thyrotoxicosis more specifically), the uptake is low because the thyroid cells are inflamed and destructed.

2/ if it is **low or normal**: it may be **factitious (exogenous)** .

Exogenous or **Ectopic** source of thyroid hormones .

MEMORISE this tumor in the ovary : **struma ovarii** (teratoma in the ovary mainly composed of thyroid tissue, so this tumor secretes thyroid hormones and causes non-central hyperthyroidism (low TSH, low uptake, low or normal thyroglobulin).

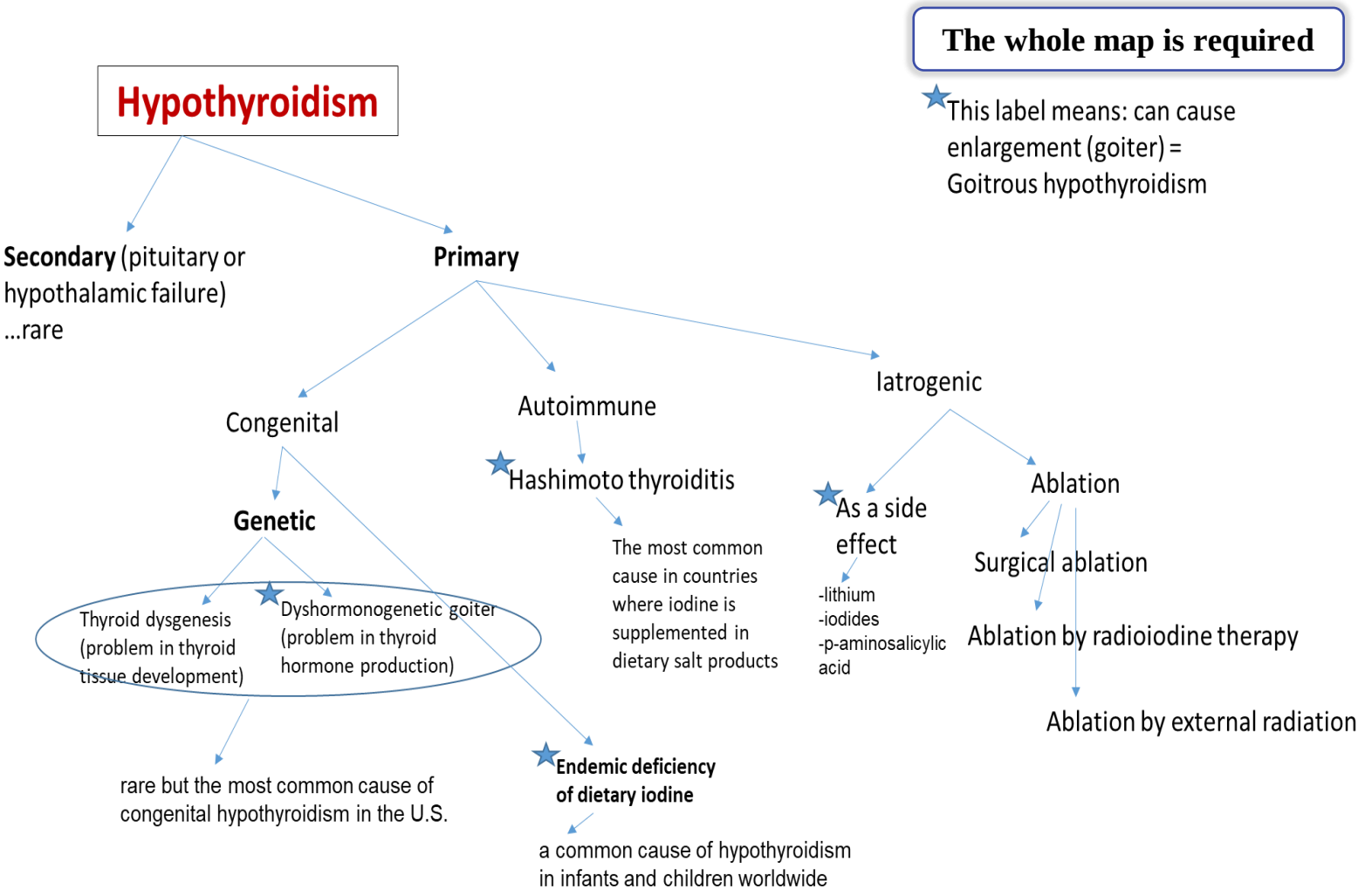
Thyroid scan is different from thyroid uptake :

- In **thyroid scan** we use a radioactive iodine or technetium and see the distribution of its uptake in the gland…it shows if a nodule is over-uptaking (a toxic adenoma for example) or homogenous over-uptake (Graves disease for example) .
- In **thyroid uptake**, we give the iodine or technetium and just count the percentage of uptake to know if high- or low uptake .

Thyrotoxicosis with high 24-h RAI uptake	Thyrotoxicosis with low 24-h RAI uptake
Graves disease	Factitious
Multinodular goiter	Subacute (painless) thyroiditis
Toxic adenoma	Granulomatous (painful) thyroiditis
	Secretion from struma ovarii (ovarian teratoma containing mostly thyroid tissue)
	Iodine-induced hyperthyroidism

Like using iodinated contrasts for imaging

Some stains that contain iodinated contrasts are used for imaging . The iodine in these contrasts can cause hyperthyroidism, the uptake is low (because the thyroid tissue is saturated with iodine) .



NOTES :

* **Secondary(central)** = pituitary or hypothalamic failure=**rare** .

* **most common cause = primary :**

1- Congenital :

1) **genetic** : **thyroid dysgenesis** (thyroid tissue isn't formed properly which causes less hormonal production) / **Dyshormonogenetic goiter** (thyroid tissue is properly formed, but is not capable of producing hormones) . (these two are the most common causes of congenital hypothyroidism in USA) .
2) **Endemic deficiency of dietary iodine** : (It's the most common cause of hypothyroidism in children worldwide) .

2- Autoimmune : **Hashimoto thyroiditis** (it primarily causes hypothyroidism, unlike other types such as de Quervain and Subacute Lymphocytic Thyroiditis) . it's the most common cause of hypothyroidism in developed countries (that have iodine supplementation in dietary salts) -we're talking about **adults mainly**- .

3- Iatrogenic (surgeries and drugs) :

1) **Drugs' side effects** : **lithium** (psychiatric conditions), **iodides** (not iodine), **p-aminosalicylic acid** .
2) **Ablation : surgical** (thyroidectomy), **radioiodine** (while curing hyperthyroidism or thyroid tumor), **external radiation** (e.g. lymphoma in the neck affects the thyroid and leads to hypothyroidism).

Goiter : thyroid enlargement , it can be **caused by** :

Graves (enlargement in the whole thyroid gland), toxic multinodular goiter (enlargement with multiple nodules), hypothyroidism (the labeled diseases above : goitrous hypothyroidism) .

Clinical manifestations of hypothyroidism :

Cretinism in infancy or early childhood and **myxedema** in older children and adults .

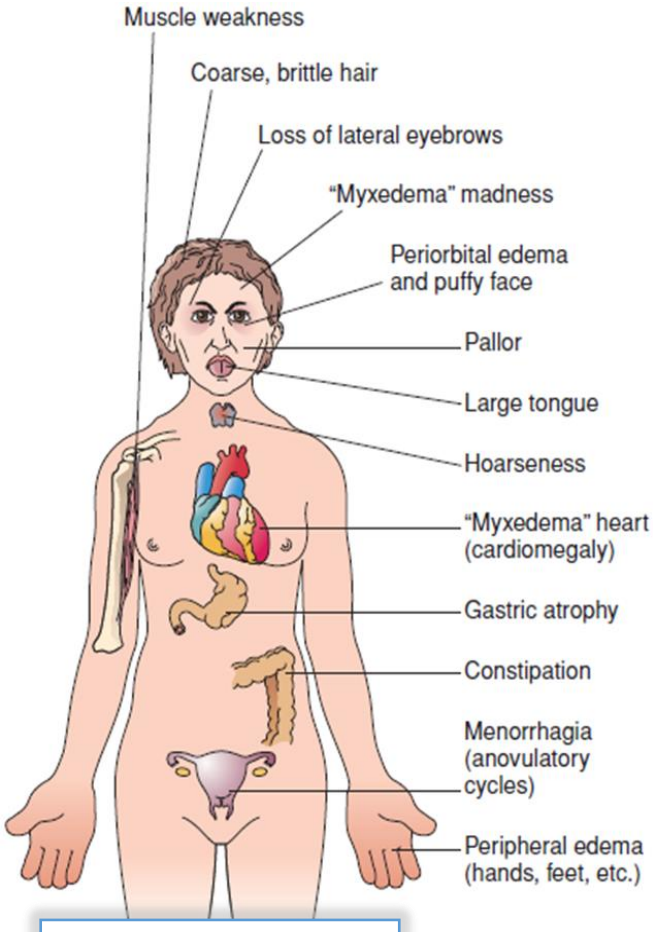
- **-Protruding tongue**
- **-Growth retardation with short limbs**
- **-Coarse dry skin**
- **-Lack of hair and teeth**
- **-Mental deficiency (retardation)**
- **-Pot belly**
- **-Often umbilical hernia**
- **-Hypotonia (decreased muscle tone)**

Myxedema : Glycosaminoglycans accumulate in the tissues with associated water and cause myxedematous fluid accumulation .

Myxedema madness : psychosis, depression

Menorrhagia : lack of thyroid hormones will cause coagulation problems so bleeding will increase .

Amenorrhea may occur (T3 and T4 decrease so TRH increases from the hypothalamus and this induces the pituitary gland to secrete prolactin which causes amenorrhea) .



The doctor mentioned all symptoms in this picture.

- **Hyperthyroidism female patient → amenorrhea (unclear reason) .**
- **Hypothyroidism female patient → menorrhagia (and sometimes amenorrhea) .**

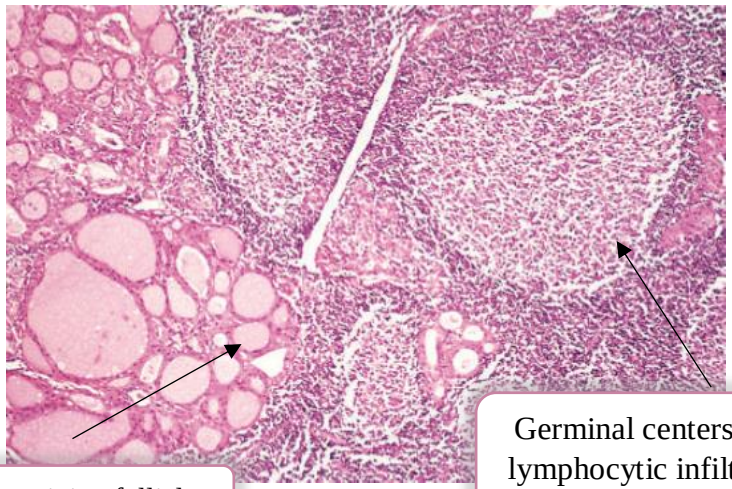
Thyroiditis :

The manifestations range from thyrotoxicosis to euthyroid state (neither increase nor decrease) and *to a lesser extent* to hypothyroidism (with de quervain and subacute lymphocytic thyroiditis, there's destruction in thyroid tissues).

1) Chronic lymphocytic (Hashimoto) thyroiditis :

(mainly causes hypothyroidism, if it caused thyrotoxicosis >> hashitoxicosis) .

- Mainly 45-65 years, but any age .
- Females more .
- CD8, CD4, IFN-gamma, other cytokines, macrophages, **antibodies** : (anti-thyroglobulin, anti-thyroid peroxidase) .
- **Goiter** with too many lymphocytes (attacking the tissues) including germinal centers with **destruction** of thyroid follicles, **Hurthle** (oxyphilic=oncocytic) cell change (cytoplasm of the follicular epithelial cells is bulky, eosinophilic and finely granular) and **fibrosis**…may end with **atrophy** .
- CTLA-4 mutations (**autoimmune**) .



Patients with Hashimoto thyroiditis often have other autoimmune diseases (there's an association between autoimmune diseases) and are at increased risk for the development of B-cell non-Hodgkin lymphomas in thyroid.

Patients with Hashimoto thyroiditis often have increased risk for the development of MALTOMA (extranodal marginal zone B-cell lymphoma), which is also seen in Sjogren's syndrome (salivary) and stomach maltoma (caused by H.pylori) .

2) Subacute Granulomatous (de Quervain/painful) Thyroiditis :

- 30-50 years
- Females more
- Viral infection-induced

…**not** autoimmune

- A majority of patients have a history of an upper-respiratory infection Shortly before the onset of thyroiditis
- **painful**
- usually **self-limited** (thyrotoxicosis occur then eurothyroid state, and rarely hypothyroidism) .
- destroyed follicles, extravasated colloid with exuberant **granulomatous** Reaction .

3) Subacute Lymphocytic (Painless) Thyroiditis :

- Sometimes after delivery (**postpartum** thyroiditis) .
- **Autoimmune** (antithyroid antibodies in majority of patients) .
- middle-aged women .
- usually self-limited .

De Quervain thyroiditis + subacute lymphocytic thyroiditis mainly cause thyrotoxicosis .

4) Riedel Thyroiditis :

- **extensive fibrosis** (hard and extending to the neck) involving the thyroid and contiguous neck structures .
- an **IgG4-related** disease .

In adults (clinically) it could be mistaken for a tumor in the thyroid (pleomorphic carcinoma, undifferentiated carcinoma..), but we differentiate it by the extensive fibrosis + it's an IgG4-related disease .

IgG4-related diseases : a group of diseases with IgG4 antibodies involved in the pathogenesis (such as autoimmune pancreatitis and Riedel thyroiditis) .

Graves disease : (the most common cause of primary hyperthyroidism)

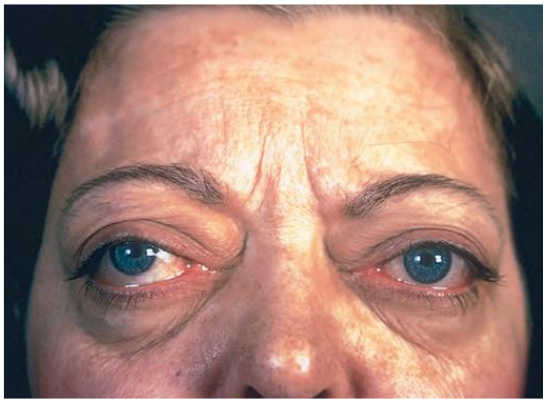
Diffuse goiter (homogenous) + **thyrotoxicosis** + (in 40%) infiltrative **ophthalmopathy** (exophthalmos=gaze) + (in a **minority** of patients) infiltrative dermopathy (**pretibial myxedema**: fluid accumulation with glycosaminoglycans on the leg in front of the tibia) .

Myxedema mainly occurs in **hypothyroidism**, but in some cases of graves it occurs as pretibial myxedema.

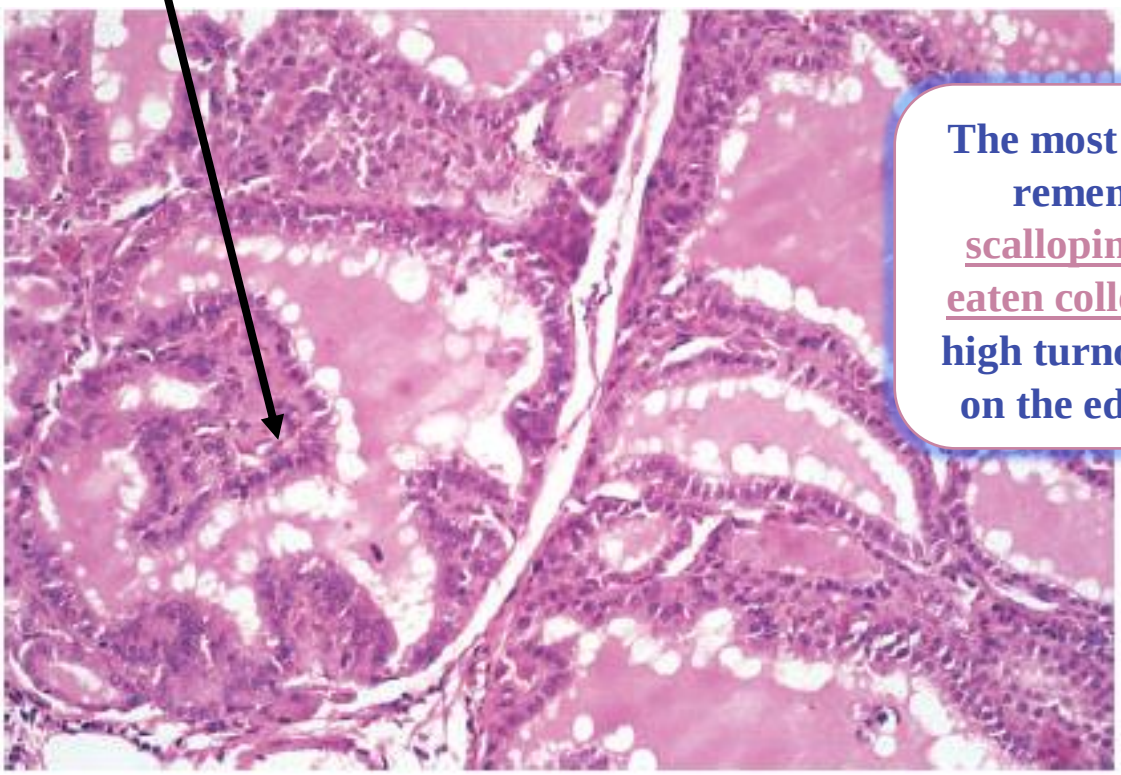
- 20-40 years
- Women more
- 1.5% to 2% of women in the United States…**not uncommon**
- Genetic predisposition (**autoimmune**) : **HLA-DR3, CTLA-4 & PTPN22**
- Elevated **antibodies**:
  1) **TSI** (thyroid-stimulating immunoglobulin) → it stimulates the receptors of TSH → increase thyroid hormones → thyrotoxicosis -or hyperthyroidism- (stimulatory type hypersensitivity reaction = antibody stimulates the tissue instead of attacking and defense) .
  TSI is an **IgG .** it's **specific and sensitive** & in all patients .

2) **Thyroid growth-stimulating immunoglobulins .**
3) **TSH-binding <u>inhibitor</u> immunoglobulins :** (the opposite, which explains the attacks of hypothyroidism that occur sometimes) .

- **Exophthalmos** is caused by retroorbital (behind the eye) Inflammation & increased retroorbital connective tissue/glycosaminoglycans, muscle & fat, and all of these push the eye outward (gaze) .
- **Associated with other autoimmune diseases .**



*** Pseudopapillae (no fibrovascular cores)**



Graves disease. The follicles are lined by tall columnar epithelial cells that are actively resorbing the colloid in the centers of the follicles, resulting in a "scalloped" appearance of the colloid.

The most important thing to remember here is the <u>scalloping of colloid (muth eaten colloid)</u>, because of the high turnover (white bubbles on the edges of the colloid).

*** Hypertrophy & hyperplasia of follicular epithelial cells .**

Goiter : (thyroid enlargement)

-Regarding the previously mentioned goitrous diseases (other than Graves): Early in goiter development, **TSH-induced hypertrophy and hyperplasia** of thyroid follicular cells usually result in diffuse, symmetric enlargement of the gland (**diffuse goiter**)

-Virtually all long-standing diffuse goiters **convert into multinodular goiters** .

(When the reason is **iodine deficiency**) :

Less iodine → no thyroid hormones → hypothyroidism → feedback inhibition on the pituitary gland → more TSH → hypertrophy and hyperplasia of the thyroid cells (it's not secreting hormones, but it's getting bigger) → **Goiter**

=Not toxic

Multinodular goiters typically are hormonally silent, but a minority (approximately 10% over 10 years) manifest with thyrotoxicosis secondary to the development of autonomous nodules that produce thyroid hormone independent of TSH stimulation. This condition, known as *toxic multinodular goiter* or *Plummer syndrome*, is not accompanied by the infiltrative ophthalmopathy and dermopathy of Graves disease–associated thyrotoxicosis. The incidence of malignancy in long-standing multinodular goiters is low (<5%) but not zero, and concern for malignancy arises with goiters that demonstrate sudden changes in size or associated symptoms (e.g., hoarseness).

Mainly follicular carcinoma

High uptake with multiple spots

Some of the nodules (because of the TSH effect) may grow and cause large hyperplasia with mutations, so it becomes irresponsive to TSH, and with a little supply of iodine, the nodules will have higher activity

+ It's not accompanied by pretibial myxedema

Clinical manifestations:

These two manifestations often come with cancer, but goiter can cause them too .

- **Cosmetic problem** of a large neck mass .

- It may cause **airway obstruction** or **dysphagia** .

- It may cause **compression of large vessels** in the neck and upper thorax → congestion in the blood vessels of the face (so-called "**superior vena cava syndrome**") .

Thank you