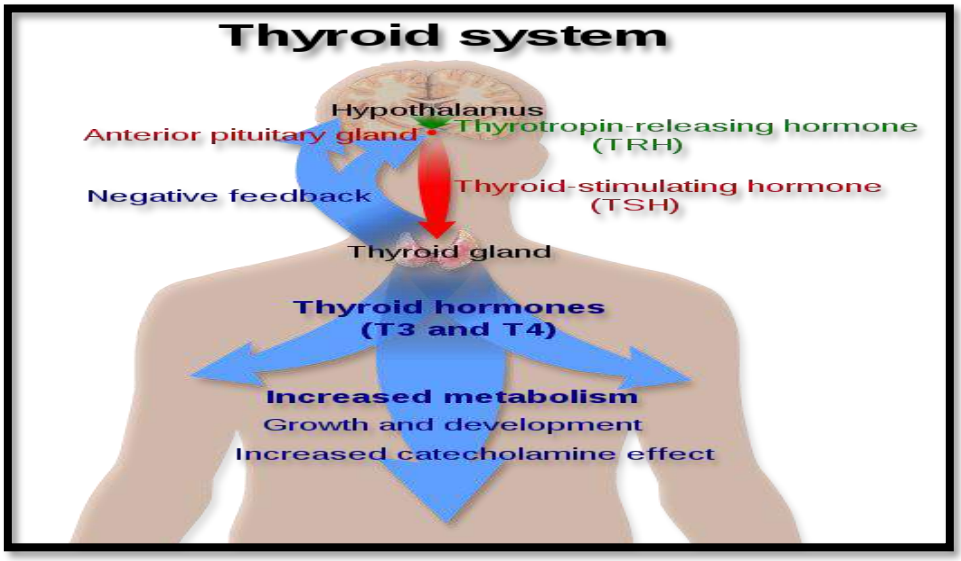
Lecture No. 25-26

Thyroid gland

The human thyroid gland is a major component of the endocrine system. Thyroid hormones perform many important functions. They exert powerful and essential regulatory influences on growth, differentiation, cellular metabolism, and general hormonal balance of the body, as well as on the maintenance of metabolic activity and the development of the skeletal and organ system.

The hormones Thyroxine (T4) and Triiodothyronine (T3) are secreted from the thyroid gland and regulated by a sensitive feedback system involving the hypothalamus and pituitary gland. The hypothalamus is an endocrine gland in the brain releases the thyrotropin releasing hormone (TRH), which stimulates the pituitary to release the thyroid stimulating hormone (TSH). This causes the thyroid to release T3 and T4 and these in turn regulate the release of TRH and TSH via a feedback control mechanism.



Synthesis of T3 and T4

Thyroglobulin (Tg) is a large tyrosine-rich protein bind to iodine after oxidation of iodide, a reaction catalysed by thyroid peroxidase (TPO) and release monoiodotyrosin (MIT) and di-iodotyrosine (DIT). Then peroxidase links 2 DIT to form T4 or one DIT and one MIT to form T3 released by thyroid gland cells in the circulation. In liver deiodinases enzymes covert about 1/3 of the T4 into T3.

Oxidation

Iodide $\xrightarrow[\text{TPO}]{}$ **Iodine +** **Thyroglobulin (Tg)** $\longrightarrow$ **Monoiodotyrosin + Di-iodotyrosine**

Monoiodotyrosine + Diiodotyrosine $\longrightarrow$ **Triiodothyronine (T3)**

Diiodotyrosine + Diiodotyrosine **Thyroxine (T4)**

T4 and T3 may stay free in plasma or bind to several serum proteins mainly; thyroid binding globulin (TBG), transthyretin and albumin. Only about 0.02% of T4 and 0.3% of T3 is free in plasma.

Thyrotoxicosis is a characteristic feature of overproduction of the thyroid hormone; Thyroxine (T4) and Triiodothyronine (T3). This is known as hyperthyroidism in which the level of these hormones increased above normal level of blood. Thyrotoxicosis can occur for other reasons as ingestion of exogenous thyroid hormone as tablets, toxic thyroid adenoma, thyroiditis and anti-arrhythmic drug.

Autoimmune thyroid disease is broadly classified into categories on the basis of the effect on gland function: **autoimmune hyperthyroidism** is seen in **Graves's disease** and **hypothyroidism** is seen in **Hashimotos thyroiditis**.

Patient's serum also containing different types of auto-antibody that directed against different thyroid self antigens mainly Tg, Tpo, thyroid growth stimulating Ig (TGI) and thyroid stimulating hormone receptor (TSH-R).

Two types of anti-TSH-R antibodies may exist in the patient serum:

1. Stimulatory (Thyroid Stimulating Ig or TSI).
2. Blocking or inhibitory (Thyroid Binding Inhibitory Ig or TBII).

Graves's disease

It is the most common cause of hyperthyroidism which driven by an autoimmune mechanism. Graves's disease has a peak incidence in the 3rd and 4th decades and is found in approximately 0.1-0.5 % of the general population. It is more common in women than man (7:1). Predispositions to Graves's disease include living in an area of high iodine intake, female sex, stress and possession of HLA-DR3, which confer a relative risk of disease.

In Graves's disease the dominant type of anti-TSH-R Abs is the TSI, however, the presence of both types of Ab (TSI &TBII) in some patients may explain the fluctuation from over activity to under activity of the gland. The TSI mimic the TSH in its action, even more, it has a more prolonged action on the activation of thyroid gland cells than TSH do.

Pathogenesis of Graves's disease depends on the humoral and cell-mediated immunity participation. However, T cells (T_H2, $CD8^+$) are responsible for the glandular thyroid T cells infiltration, whereas the antibodies are acting as a disturbing factor for the normal physiological function of the gland. A clear application for that is the autoimmune

syndrome in neonates which is caused by the transplacental transfer of IgG which cause a transient disturbance in the endocrine physiology that disappears with time after birth in proportion with the half-life time of IgG without any significant damage of the target organs.

The level of thyroid Abs in pregnant women with **Graves's disease** and **Hashimotos thyroiditis** decreased during pregnancy, but increased again after word.

Symptoms

Patients typically present with the symptoms or signs of hyperthyroidism (palpitations, tachycardia, arrhythmias, heat intolerance, increased appetite with weight loss, diarrhea, weakness and proximal myopathy, nervousness and tremor). One characteristic feature of Graves's disease is eye disease characterized by protrusion of the eyeball and lid retraction resulting from tissue inflammation in the retro-orbital space. Goiter which is an enlargement or hypertrophy of the thyroid tissue is of diffuse pattern in Graves's disease.

Diagnosis

Laboratory findings are of

1. Elevated thyroid hormones- thyroxine (T4) and triiodothyronine (T3)- with suppressed levels of thyroid stimulating hormone(TSH).
2. Measuring of auto-Abs

- Anti-TSH-R in most case (TSI, TGI).
- Anti-TPO in 50% of cases (more common in **Hashimotos thyroiditis)** and anti-Tg in lesscases.
- Thyroid growth stimulating Ig (TGI) is seen in the serum of Graves's disease patient with goiter and in some patients with toxic multinodula and non-toxic goiter. The titer of these Ab is correlated with the size of goiter, but not associated with the level of T4 and T3 as the case with TSI in which there is strong association between the high level of T4 and T3 and the level of TSI.

3. The radioactive iodine uptake test and thyroid scan test. The uptake test uses radioactive iodine (I-123) injected or taken orally on an empty stomach to measure the amount of iodine absorbed by the thyroid gland. Person with hyperthyroidism absorb too much iodine. The thyroid scan producing images is typically conducted in connection with the uptake test to allow visual examination of the over-functioning gland.

Hashimotos thyroiditis

Hashimotos thyroiditis (autoimmune thyroiditis) is a chronic disease typically characterized by enlargement (goiter) and dense lymphatic infiltration of the thyroid gland. It is four times more common in women and has incidence of approximately 0.5% in the general population; the incidence peaks in middle age.

Causes

- HLA-DR5 gene most strongly implicated conferring a relative risk. In addition, HT may be associated with polymorphism of CTLA-4 gene.
- Environmental factors (high iodine intake, infection as chronic HCV, certain drugs, exposure to radioactive isotypes, presence of other autoimmune diseases as celiac disease and type 1 diabetes.

Pathogenesis of **Hashimotos thyroiditis** depends on the humoral and cell-mediated immunity participation. However, T cells ($CD4^+$ (T_H1), $CD8^+$) are responsible for the destruction of thyroid tissue that targeting the auto antigens Tg and Tpo. Microbial mimicry by viral or bacterial antigens may drive this destructive mechanism.

Symptoms

Patients usually complain of goiter as the main symptom, with an enlarged, firm, sometimes nodular thyroid gland on examination. At presentation, patients may still be euthyroid, but with time the pathological processes result in loss of thyroid tissue and hypothyroidism. Symptoms and signs of hypothyroidism may be seen at the first consultation (fatigue, cold intolerance, dryness of skin, anorexia, weight gain, menstrual disturbance, huskiness of voice, mental slowing, abnormal reflexes).

Diagnosis

1. Low level of free T3 and free T4.
2. Low level of total T3 and free T4.
3. High level of TSH.
4. Measuring of auto-Abs
   - Anti-Tg Ab is found in 90% of cases.
   - Anti-TPO Ab correlate with the severity of the disease.

   Both Abs contribute in decreasing the uptake of iodine leading to hypothyroidism.

- Other auto-Ab are detected (anti- TSH-R blocking Abs(low), anti-thyrotropin-R Ab, anti-second colloid Ag) these antibodies have an inhibitory effect on the production of the thyroid hormones.

Graves's disease	Hashimotos thyroiditis
1. Hyperactivity	1. Fatigue, lethergy
2. Weight loss with increase of Appetite	2. Weight again
3. Heat intolerance	3. Cold intolerance
4. Thirst/polyuria	4. Dry coarse skin
5. Diffuse goiter	5. Rubbery, nodular goiter
6. Ophthalamopathy, eyelid Retraction, exophthalmous, peri-orbital odema	6. Facial edema (myxodema)
7. Tachycardia	7. Mostly bradycardia
8. Free T3 ↑ Free T4 ↑ Total T3 ↑ Total T4 ↑ Anti-Tg N(rarely ↑ in few cases) Anti-TPO N (slightly in 50% of cases) Anti-TSH-R ↑ TSH ↓	8. Free T3 N- ↓ Free T4 ↓ Total T3 N- ↓ Total T4 ↓ Anti-Tg ↑ Anti-TPO ↑ Anti-TSH-R N TSH ↑
9. Treatment Anti-thyroid drugs Radioactive iodine Thyroidectomy	9. thyroxine
10. TH2	10. TH1

Lecture No. 27-28

Tumor

Tumor is an overgrowth (uncontrolled growth) of tissues and cells in certain organs in the body which result in a mass of tissue that has result in destruction of normal architecture of the tissue and lost the normal function of the healthy original tissue.

Tumor can be generally classified into

1. **Benign tumor:** cluster of tumor cells that are localized in a restricted area in the body without the ability to move to other areas in the body.
2. **Malignant tumor:** cluster of tumor cells that can move and invade (**metastasis**) other adjacent and far away tissues.

Metastasis means spreading of the invasion tumor cells from the primary focus of tumor to other parts of the body via blood or lymph circulation to form a secondary focus of tumor.