The Immune System & Endocrine Disorders

Lecture 1

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Explanation & Extra Notes

Objectives

- Recognize the relation of endocrine disorders and autoimmunity.
- Understand the mechanisms of damage which take place at endocrine glands and their consequences.
- Know the important examples of autoimmunity which affect different endocrine glands and the pathogenesis of these disorders.

Introduction

- Many endocrine disorders are *organ-specific* autoimmune diseases.
- **Organ-specific autoimmune disease:** the immune response is directed to a target antigen unique to a single organ.
- The manifestations are largely limited to that organ.
- The damage may be directly by: **Humoral (Antibodies) Immunity** or **Cell-mediated Immunity (CMI)**.
- The antibodies may **over stimulate or block** the normal function of the target organ.

Autoimmunity doesn't always effects the function.

Examples Of Autoimmune Endocrine Diseases

Thyroid

- **Hashimoto's disease:** autoantibodies against *thyroid peroxidase*
- **Primary myxoedema:** atrophy of the thyroid
- **Graves' disease:** Autoantibodies against *thyroid stimulating hormone receptor* (TSH-R)

Pancreas

- **Type 1 Diabetes**

Adrenal gland

- **Addison's disease:** chronic endocrine disorder. The glands produce insufficient *steroid hormones*

Gonads

- **Autoimmune oophoritis:** inflammation of *ovaries*
- **Autoimmune orchitis**: *testicular* pain involving swelling, inflammation and infection.

Pituitary

- **Lymphocytic hypophysitis:** low production of one or more hormones by the pituitary gland due to autoantibodies and autoimmunity

Thyroid Autoimmunity

- **Hypothyroidism**
  - Hashimoto's disease
  - Atrophic thyroiditis
- **Hyperthyroidism**
  - Graves' disease

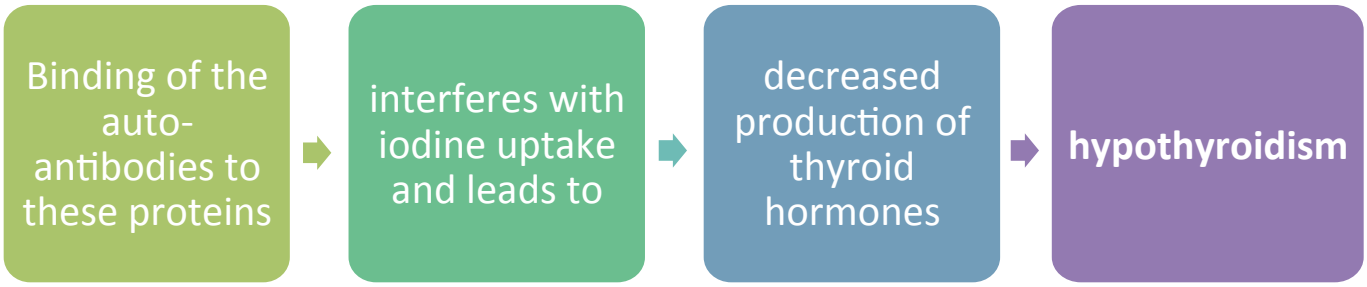
Chronic Lymphocytic Thyroiditis (Hashimoto's)

- Male: Female ratio is **1:3**
- Frequently seen in **middle-aged women**.
- Associated with **HLA-B8**
- Individuals produce auto-antibodies and sensitized **TH1 cells** specific for thyroid antigens.
- **Anti-peroxidase** and **anti-thyroglobulin** antibodies.
- There will be symptoms of **hypothyroidism.**
- **The DTH response is characterized by:** an intense infiltration of the thyroid gland by lymphocytes, macrophages, and plasma cells, which form *lymphocytic follicles* and *germinal centers.*

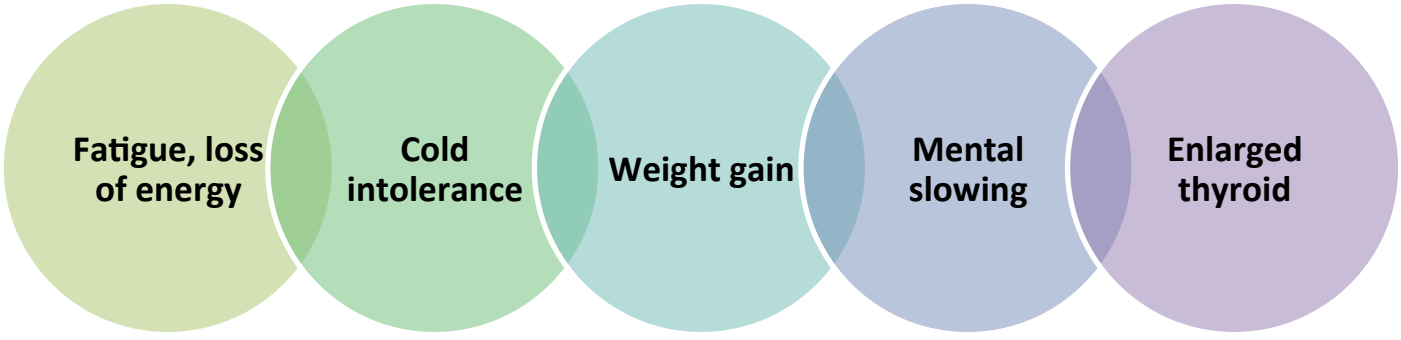
- **The resultant inflammatory response causes:** A goiter or visible enlargement of the thyroid gland (a physiological response to hypothyroidism).

- **Antibodies are formed to a number of thyroid proteins, including:**
  - thyroglobulin
  - thyroid peroxidase

(both of which are involved in the uptake of *iodine*)



Clinical Features of Hashimoto's

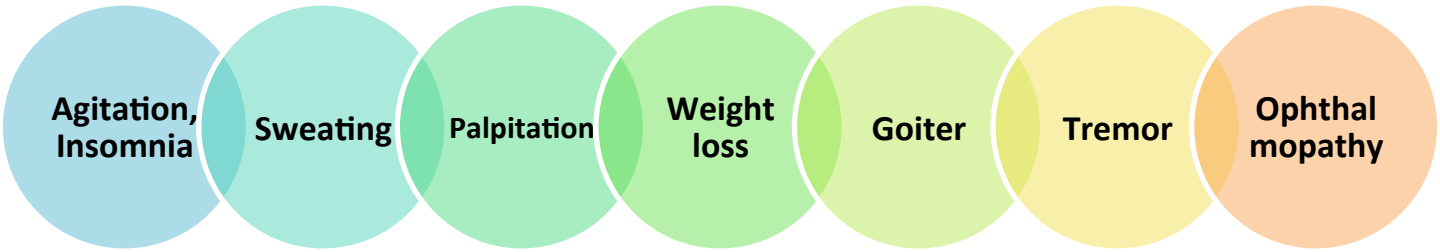


Graves's Disease

- Less common than Hashimoto's disease.
- Male: Female ratio up to **1:7**
- Associated with **HLA-B8**
- The production of thyroid hormones is carefully regulated by *thyroid-stimulating hormone* (TSH), which is produced by the pituitary gland.
- **Normally:** Binding of TSH to a receptor on thyroid cells activates **adenylate cyclase** and stimulates the synthesis of two thyroid hormones, **thyroxine** and **triiodothyronine**.
- **In Graves' disease:** *auto-antibodies* bind the receptor for TSH and mimic the normal action of TSH, activating adenylate cyclase and resulting in production of the thyroid hormones.
- **But unlike TSH:** the autoantibodies are not regulated, and consequently they **overstimulate** the thyroid and cancels negative feedback.
- That's why these auto-antibodies are called **long-acting thyroid-stimulating (LATS) antibodies.**

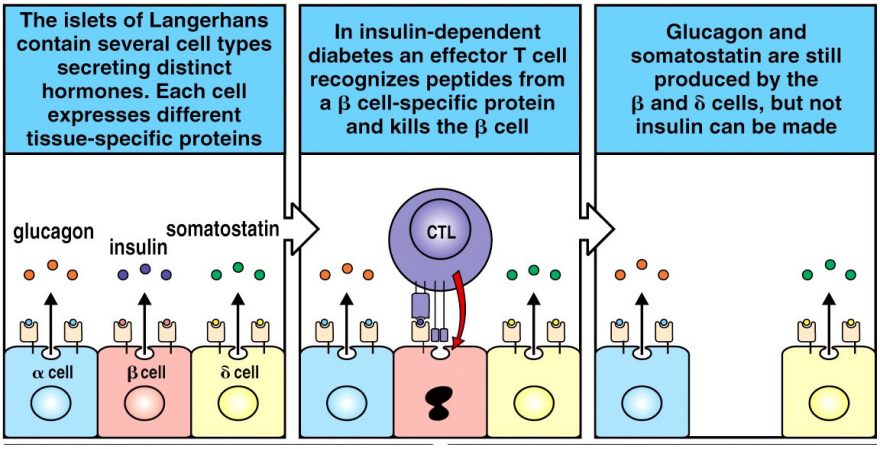
Summary: The antibodies are acting like copycats of TSH.

Clinical Features of Graves'



Insulin-dependent Diabetes Mellitus (IDDM)

- IDDM is an example of type **IV hypersensitivity**.
  - Auto-reactive **T-cells** invade the *pancreatic islets* and destroy the insulin-secreting beta cells.
  - **Macrophages** become activated.
  - This is frequently referred to as **insulitis. (Cell-mediated DTH response)**
  - **As a result:** decreased production of insulin and consequently increased level of blood glucose.
- **Pathogenesis:** Mechanisms responsible for the islet cell destruction:
  - Genetic susceptibility (HLA-DQ alleles).
  - Autoimmunity.
  - Environmental factors, infections. E.g.. Coxsackie virus, Echovirus
- The most likely scenario is that **viruses** cause *mild beta cell injury*, which is followed by an **autoimmune reaction** against *altered beta cells* in persons with **HLA-linked susceptibility**.
- Type 1 IDDM patients are prone to other autoimmune disorders (10%).



Pancreatic beta-cell auto-reactive T cells **(DTH & CTL)** and autoantibodies.

Autoimmune Adrenocortical Failure (Addison's)

- Male: Female ratio is **1:4**
- Associated with **HLA-DR3** and/or **DR4**
- It is a classic **organ–specific autoimmune** disorder.
- It develops as a consequence of autoimmune destruction of **steroid-producing cells** in the adrenal gland.
- A major autoantigen is **21-hydroxylase (21OH).**
- Which is involved in the biosynthesis of **cortisol** and **aldosterone** in the adrenal cortex.
- **T cell-mediated injury** is likely to be central to pathogenesis.
- **Adrenal Autoantibodies** may have a pathogenic role, or could arise secondary to T cell-mediated tissue damage,

Clinical Features of Primary Adrenal Insufficiency

Weakness

Weight loss

Poor appetite

Confusion

Hyperpigmentation

Hypotension

Shock

Damage to the Adrenal Cortex my be caused by

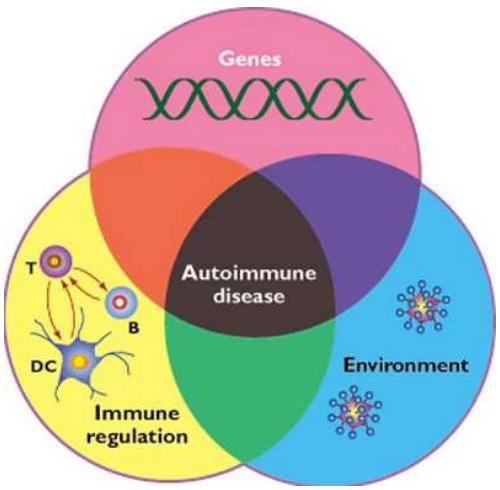
Autoimmune disease

Infections

Hemorrhage

Tumors

Drugs (anticoagulants)



Summary

	Hashimoto's	Graves'	Diabetes	Addison's
Organ	Thyroid	Thyroid	Pancreas	Adrenal
M:F Ratio	1:3	1:7	-	1:4
Gene	HLA-B8	HLA-B8	HLA-DQs	HLA-DR3 / DR4
ABs	Anti-peroxidase, Anti-thyroglobulin	Long-acting thyroid-stimulating (LATS) antibodies	T-cells	T-cells, Adrenal Autoantibodies
Cells Affected	Thyroid peroxidase	TSH-producing cells	Pancreatic islets (insulin-secreting beta cells)	Steroid-producing cells
Hormones Affected	T↓3 , T↓4	T↓3 , T↓4	Insulin	Cortisol, Aldosterone

Apologies for the delay of the teamwork.

MCQs

1. Which one of the following genes is associated with Grave's disease:

A) HLA-B4

B) HLA-B6

C) HLA-B8

D) HLA-B3

2. A patient developed a goiter after being diagnosed with Hashimoto's thyroiditis. What is the cause?

A) Inflamed lymph nodes

B) Hypoactivity of the gland

C) Tumor

D) Compensatory mechanism

3. Type 1 diabetes is an autoimmune disease with a prior infection of which kind?

A) Viral

B) Bacterial

C) Fungal

D) Protozoan

4. The enzyme affected in Addison's disease is

A) 17α -hydroxylase

B) 11-deoxycortisol

C) 21-hydroxylase

D) 11β-hydroxylase

5. In Hashimoto's, which of the following cells infiltrate the thyroid gland ?

A) Lymphocytes

B) Plasmocytes

C) Macrophages

D) All of the above

1:C, 2:D, 3:A, 4:C, 5:D