Revised & Approved

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Endocrine Disorders

Color index

Important

Extra

Notes

IMMUNOLOGY
TEAM 439

Objectives

- To recognize that many endocrine disorders are organ-specific autoimmune diseases.
- To understand the mechanisms of damage which take place at endocrine glands and their consequences.
- To know the important examples of autoimmunity which affect different endocrine glands and the pathogenesis of these disorders.

Editing File

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Dr. Mohamed Sherif

Recall (Extra)

Autoimmune disease is caused by **failure of the tolerance processes** to protect the host from the action of self-reactive lymphocytes. These diseases result from the destruction of self proteins, cells, and organs by autoantibodies or self-reactive T cells.

	Mechanisms of Autoimmunity
Sequestration	**#438:** Some self antigens are hidden in tissues and are normally not sensed by the immune system. When those self antigens are exposed to T cells (as a result of infection/trauma), an autoimmune reaction occurs. e.g. Sympathetic Ophthalmia: Trauma in one eye releases the sequestered intraocular antigens to the Lymph node (activates T cells) The T cells will then move to the undamaged eye and attack the self-antigens there.
Molecular Mimicry	**#438:** Viruses and bacteria possess similar/identical antigenic determinants to those of normal cells. e.g. Rheumatic fever
Abnormal MHC II Expression	**#438:** Abnormal expression of MHC Class II on non-APC cells (e.x. pancreatic β cells) due to IFNγ production (induced by a viral infection) causes self-reactive T cells to destroy them. e.g. Type I Diabetes
Polyclonal B Cell Activation	**#438:** Happens when a polyclonal B cell (nonspecific) is activated by certain viruses and bacteria without the help of T cells (T-independent). This self-reactive plasma cell will proliferate and eventually produce polyclonal antibodies (mainly IgM), some of which will be autoantibodies. e.g. EBV causing infectious mononucleosis

Development of autoimmunity is influenced by both genetic and environmental factors. In particular, **certain alleles of MHC (HLA genes)** have been strongly linked to autoimmunity. In addition, defects in many different genes involved in immunity can predispose individuals to autoimmune disease.

Autoimmune diseases can be broadly divided into:

1. **Systemic**: autoimmune response directed against a broad spectrum of tissues. e.g. SLE and Rheumatoid Arthritis
2. **Organ-specific**: autoimmune response directed primarily against a single organ or gland (discussed in this lecture)

Introduction: Organ-Specific Autoimmunity

- Many endocrine disorders are **organ-specific** autoimmune diseases. In 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. Defect in the gland→ Defect in all hormones associated with it
- The damage may be directly mediated by either:

Humoral (Antibodies) immunity	Cell-mediated Immunity (CMI)	Both humoral and cell-mediated immunity
the antibodies may overstimulate or block the normal function of the target organ		(e.g. **Hashimoto** and possibly Addison's)

Female Dr: It is important to know the difference between humoral and cell-mediated immunity

Humoral immunity (Antibody mediated immunity)	**Cell-mediated Immunity (CMI)**
Component of the adaptive system where B-cells are differentiated into plasma cells that can produce antibodies against specific antigens	Component of the adaptive system which involves the activation of phagocytosis, antigen specific T cells, and release of various cytokines in response to the antigen (Doesn't involve antibodies)
Mediated by B cells	**Mediated by T cells**
Acts on extracellular antigens (in the circulation or outside the infected cell)	Acts on intracellular antigens such as viruses, bacteria and parasites
Recognizes unprocessed antigens	Antigens are processed and presented by MHC complexes
Faster onset	Slower onset

Introduction: Organ-Specific Autoimmunity

➢ Examples of autoimmune endocrine diseases:

 Thyroid Diseases

- Hypothyroidism
  - **Hashimoto's disease:** Autoantibodies against thyroid peroxidase
  - Primary myxoedema also known as atrophic thyroiditis: Atrophy of the thyroid
- Hyperthyroidism
  - **Graves' disease:** Autoantibodies against Thyroid Stimulating Hormone Receptor, (TSH-R)

 Pancreas Diseases

- **Type I diabetes**

 Adrenal Diseases

- **Addison's disease**: Chronic endocrine disorder of the adrenal glands, produces insufficient steroid hormones

 Gonads Diseases

- Autoimmune oophoritis: inflammation of the ovaries
- Autoimmune orchitis: Testicular pain involving swelling, inflammation and infection

 Pituitary Diseases

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

Thyroid Diseases

Chronic Lymphocytic Thyroiditis: Hashimoto's Thyroiditis

Definition

- It is a chronic autoimmune condition characterized by immune destruction of the thyroid gland and under-reactive thyroid gland (hypothyroidism), **It is the most common cause of hypothyroidism.**
- Most prevalent in middle-aged women (Male:Female ratio is 1:3), generally speaking autoimmune diseases are more common in females than males.

HLA II Association

Dr. Adel: we don't focus on subtypes

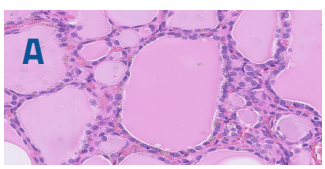
- **Predisposing effect: Associated with HLA II DR4** (DRB1*04-DQB1*03-DQA1*03)
- **Protective role: Associated with HLA II DR13** (DRB1*13-DQB1*06-DQA1*01)

(Individuals carrying predisposing effects are more vulnerable to developing the disease whereas individuals carrying the protective role are less likely to develop the disease)

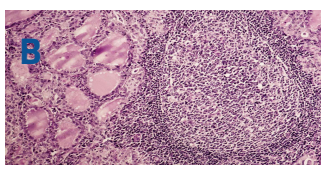
Pathophysiology

- Individuals with Hashimoto's thyroiditis produce **autoantibodies and sensitized TH1 cells specific for thyroid antigens** (specifically against certain proteins of the thyroid)
- Antibodies are formed to a number of thyroid proteins, including **thyroglobulin and thyroid peroxidase, both of which are involved in the uptake of iodine.**
- Binding of the auto-antibodies to these proteins interferes with iodine uptake, leading to **decreased** thyroid function and **hypothyroidism** (decreased production of thyroid hormones).
- The **delayed-type hypersensitivity (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. **(Reaction was elicited by Th1)**

Normal/Abnormal Thyroid



(A) Normal thyroid gland showing a follicle lined by cuboidal follicular epithelial cells



(B) Hashimoto's thyroiditis showing intense lymphocyte infiltration

In summary: CMI and humoral immune responses are activated → production of anti-thyroid peroxidase and anti-thyroglobulin → binding of autoantibodies to these proteins → interfere with iodine uptake → decreased production of thyroid hormones → hypothyroidism

Clinical Features

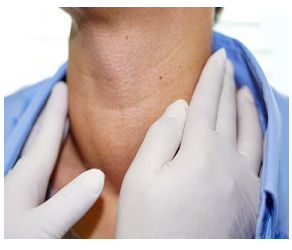
Symptoms of **hypothyroidism**:

- Fatigue, loss of energy, weight gain, cold intolerance, enlarged thyroid, and mental slowing.

The ensuing inflammatory response (DTH) causes:

- **Goiter**, or visible enlargement of the thyroid gland (a physiological response to hypothyroidism)

Goiter



Thyroid Diseases

Graves' Disease

Definition

It is an autoimmune condition that is associated with circulating TSH receptor autoantibodies leading to overstimulation of the thyroid gland with excess thyroid hormone production. It is less common than Hashimoto's disease with high female prevalence (Male: Female ratio up to 1:7).

HLA II Association

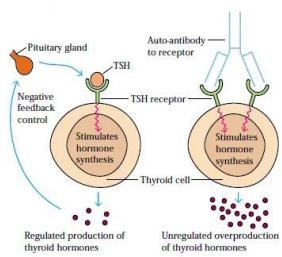
Dr. Adel: we don't focus on subtypes

- **Predisposing effect: Associated with HLA II DR3** (DRB1*03-DQB1*02-DQA1*05) **and HLA B8 (from old curriculum)**
- **Protective role: Associated with HLA II DR7** (DRB1*07-DQB1*02-DQA1*02)

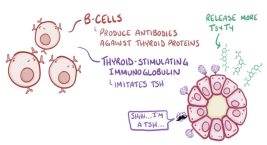
Pathophysiology

- Normal physiology: The production of thyroid hormones is carefully regulated through negative feedback by thyroid-stimulating hormone (TSH), which is produced by the pituitary gland. Binding of TSH to a receptor on thyroid cells activates adenylate cyclase and stimulates the synthesis of two thyroid hormones, thyroxine (T4) and triiodothyronine (T3).
- Graves' disease is associated with MHC II expression in thyrocytes playing a role in inducing the immune response, autoantibodies bind the receptor for TSH and **mimic** the normal action of TSH, activating adenylate cyclase and resulting in production of the thyroid hormones. Unlike TSH, the autoantibodies are **not regulated** by negative feedback and consequently they overstimulate the thyroid leading to **overproduction of Thyroid hormones: thyroxine (T4) and triiodothyronine (T3).**

Stimulating Autoantibodies



In graves disease, binding of autoantibodies to the receptor for TSH induces unregulated activation of the thyroid, leading to overproduction of TH (purple dots)



- For this reason these autoantibodies are called: long-acting thyroid-stimulating (LATS) antibodies. (Also known as Thyroid Stimulating Hormone Receptor, TSH-R)

In summary: B and T cell-mediated autoimmunity → production of stimulating antibody against TSH-receptor → ↑ thyroid function and growth → hyperthyroidism and goiter

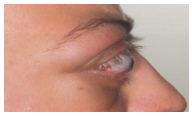
Clinical Features

Symptoms of **hyperthyroidism**:

- **Weight loss** despite increased appetite
- Diffuse **Goiter,** thyrotoxicosis
- Agitation, sleep disturbance (hyperactive)
- Sweating, palpitations
- Muscle weakness
- Tremor

Goiter

Ophthalmopathy



Specific symptom of Graves disease:

- **Ophthalmopathy** (Exophthalmos is seen: protrusion of eye, due to autoantibodies directed to antigens expressed on the retro orbital CT)

Pancreas Diseases

Insulin-Dependant Diabetes Mellitus (Type I)

Definition

A chronic condition caused by an autoimmune attack against insulin-producing cells (beta cells) scattered throughout the pancreas → insulin deficiency, hyperglycemia. **IDDM is an example of type IV hypersensitivity (Delayed type hypersensitivity).** Male to female ratio is almost 1:1, equal prevelance.

HLA II Association

- **Susceptibility genes** (Predisposing effect)**: Associated with HLA II DQ alleles**

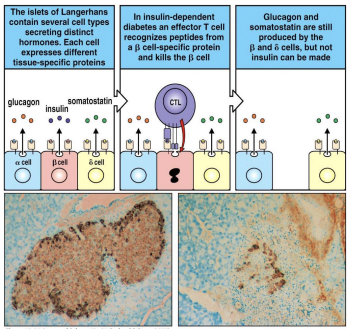
Pathophysiology

- Three mechanisms are responsible for the islet cell destruction:
  - Genetic susceptibility (HLA-DQ alleles)
  - Autoimmunity
  - Environmental factors. Infections: Coxsackie virus, Echovirus

The most likely scenario: Viral infections cause mild beta cell injury, which is followed by an autoimmune reaction against altered beta cells in people with HLA-linked susceptibility.

- **Autoreactive T-cells, cytotoxic T lymphocytes (CTL)** CD8+ , invade the pancreatic islets and destroy β cells (insulin-secreting cells) → Macrophages are activated, frequently referred to as insulitis → cytokine release including IFN-γ and **production of β islet cell autoantibodies** → Cell-mediated DTH response **(Type IV hypersensitivity response)**
  - As a result: decreased production of insulin and consequently increased levels of blood glucose (hyperglycemia)

Cellular Destruction



Pancreatic β cells, autoreactive T-cells (DTH & CTL) and autoantibodies all play a role in the cellular destruction

#436: β cells improperly express of class II (remember that β cells aren't APCs, so it's abnormal), cell antigens in beta cells then will be presented. T-cells (TH1) will come and attack the β cells. What makes β cells express abnormal class II MHC? Macrophages, produced IFN-γ which upregulates Class II MHC expression. IFN-γ produced might be triggered by the viral infection.

Complications

- Approximately 10% of Type 1 IDDM patients are prone to other autoimmune disorders

Adrenal Diseases

Autoimmune Adrenocortical Failure: Addison's Disease

Definition

- It's an endocrine disorder characterized by **chronic primary adrenal insufficiency** due to bilateral adrenal cortex destruction. Adrenal cortex destruction (destruction is usually due to autoantibodies) → ↓ production of adrenocortical hormones → glucocorticoid, mineralocorticoid, androgen deficiency. Most prevalent in females (Male:Female ratio is 1:4)

HLA II Association

Dr. Adel: we don't focus on subtypes

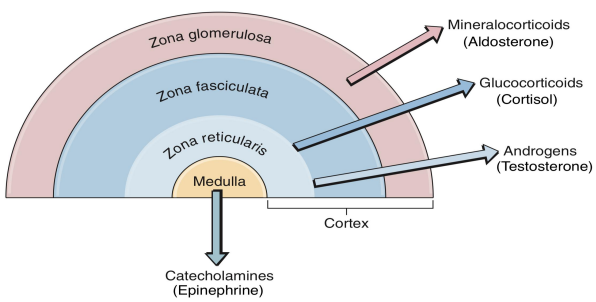
- **Susceptibility genes (Predisposing effect): Associated with HLA DR3 and/or DR4.** The most strongly associated DRB1*04 allele is DRB1*04:04

Etiology

Damage to the adrenal cortex **may be** caused by (can be more than one cause):

1. **Autoimmune disease**
2. Infections (Tuberculosis)
3. Tumors (Metastatic carcinoma)
4. Hemorrhage
5. Use of drugs (**anticoagulants**)

Adrenal Gland



Female Dr: you should know the hormones secreted from each layer (MCQs)

Pathophysiology

- It's a prototypical organ–specific autoimmune disorder.
- Develops as a consequence of autoimmune destruction of steroid-producing cells in the adrenal gland.
- **A major autoantigen is 21-hydroxylase (21OH)**, which is an enzyme involved in the biosynthesis of **cortisol & aldosterone in the adrenal cortex.**
  (What is the marker of Autoimmune Addison Disease? Anti-21-hydroxylase autoantibodies)
- T cell-mediated injury is likely to be central to pathogenesis (21 Hydroxylase-specific Cytotoxic T cells).
- Adrenal autoantibodies may have a pathogenic role (unclear yet) or could arise secondary to T-cell tissue damage.

Clinical Features

Symptoms and physical findings in Primary adrenal insufficiency (Addison Disease)

- Weakness
- Weight loss
- Poor appetite
- Confusion
- **Hyperpigmentation**
- Hypotension
- Weak pulses
- Shock

EXTRA

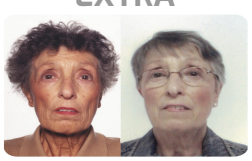


Figure 13.1 An example of increased skin pigmentation in an individual with Addison's disease (left) and resolution post-treatment (right).

Summary

	Hashimoto's	Graves'	IDDM	Addison's
Organ	Thyroid	Thyroid	Pancreas	Adrenal cortex
M:F Ratio	1:3	1:7	1:1	1:4
Susceptibility gene	HLA-DR4	HLA-DR3	HLA-DQ	HLA-DR3 and/or DR4
Immune effector (Mostly autoantibodies)	**TH1 cells** Anti-thyroid peroxidase autoantibodies antithyroglobulin autoantibodies	LATS antibodies (Also Known as TSH-R)	**TH1 cells** β islet cell autoantibodies	Anti-21-hydroxylase autoantibodies
Autoantigen (self antigen/target)	Thyroid proteins and cells	Thyroid-stimulating hormone receptor	Pancreatic beta cells	Steroid-producing adrenal cells (cortex cells)
Hormones affected	↓T3 and ↓T4	↑T3 and ↑T4	↓Insulin	↓Cortisol and ↓aldosterone

	Pathophysiology
Hashimoto's	CMI and humoral immune responses are activated → production of anti-thyroid peroxidase and anti-thyroglobulin → binding of autoantibodies to these proteins → interfere with iodine uptake → decreased production of thyroid hormones → hypothyroidism → **DTH response (Type IV hypersensitivity)**
Graves'	B and T cell-mediated autoimmunity → production of stimulating antibody against TSH-receptor → ↑ thyroid function and growth → hyperthyroidism and goiter
IDDM	Autoreactive T-cells, cytotoxic T lymphocytes (CTL), invade the pancreatic islets and destroy β cells (insulin-secreting cells) → Macrophages are activated, frequently referred to as insulitis → cytokine release including IFN-γ and production of β islet cell autoantibodies → **Cell-mediated DTH response (Type IV hypersensitivity response)** → hyperglycemia
Addison's	A major autoantigen is 21-hydroxylase (21OH), an enzyme involved in the biosynthesis of cortisol & aldosterone in the adrenal cortex. (Marker of Autoimmune Addison Disease: Anti-21-hydroxylase autoantibodies). T cell-mediated injury is likely to be central to pathogenesis (21 Hydroxylase-specific Cytotoxic T cells).

QUIZ

Q1) Which pancreatic cells are destroyed by autoreactive T cells in Insulin-Dependant Diabetes Mellitus?

A	Alpha cells	B	Beta cells	C	Gamma cells	D	Delta cells

Q2) Long acting thyroid stimulating antibodies are present in which disease?

A	Hashimoto's Disease	B	Graves' Disease	C	Addison's Disease	D	IDDM

Q3) Anti-21Hydroxylase autoantibodies are markers of which disease?

A	Hashimoto's Disease	B	Graves' Disease	C	Addison's Disease	D	IDDM

Q4) Which of the following is has a predisposing affect in Chronic Lymphocytic Thyroiditis: Hashimoto's Thyroiditis?

A	HLA-DR3	B	HLA-DR4	C	HLA-DR7	D	HLA-DR13

Q5) Which of the following hypersensitivity responses is seen in Insulin-Dependant Diabetes Mellitus?

A	Type I	B	Type II	C	Type III	D	Type IV

Q6) Which of the following hypersensitivity responses is seen in Hashimoto's Thyroiditis?

A	Type I	B	Type II	C	Type III	D	Type IV

Q7) Which of the following is has a protecting affect in Chronic Lymphocytic Thyroiditis: Hashimoto's Thyroiditis?

A	HLA-DR3	B	HLA-DR4	C	HLA-DR7	D	HLA-DR13

Q8) Which of the following is has a predisposing affect in Insulin-Dependant Diabetes Mellitus?

A	HLA-DR3	B	HLA-DR4	C	HLA-DQ	D	HLA-DR13

Q9) Which of the following is has a predisposing affect in Graves' Disease?

A	HLA-DR3	B	HLA-DR4	C	HLA-DR7	D	HLA-DR13

Q10) Anti-thyroid peroxidase and anti-thyroglobulin autoantibodies are markers of which disease?

A	Hashimoto's Disease	B	Graves' Disease	C	Addison's Disease	D	IDDM

Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10
B	B	C	B	D	D	D	C	A	A

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