Immunology team 431

(The Immune System and Endocrine Disorder)

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Red➔ important

Green+blue➔Team's notes and explanation

Immune response against endocrine glands

- Is **organ-specific autoimmunity**(not systemic, immune system only targets a single organ not system)
- Both **cellular** and **antibody mediated**(humoral) immune responses are involved
- Manifestations are usually related to the organ involved (Single or multiple organ involvement)

Autoimmune polyendocrine syndrome type

- It is charaterized by **multiple endocrine glands dysfunction as a result of autoimmunity** and is associated with:
  - Hypoparathyroidism (Hypocaclaemia)
  - Addison's disease (Hypoglycemia, hypotension)
  - Hypothyroidism
  - Hypogonadism and infertility
  - Vitiligo (depigmentation of the skin)
  - Alopecia (baldness)
  - Malabsorption
  - Pernicious anemia
  - Chronic active (autoimmune) hepatitis
  - Diabetes (Type 1)

Different combination are found with different types of these syndromes but they are mostly related to theses organs:

And many diseases may be involved

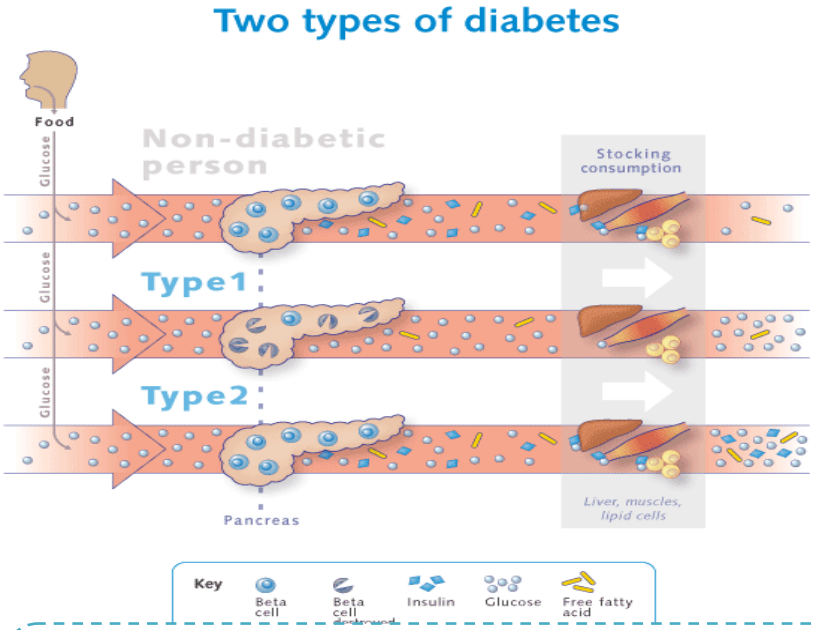
Condition that causes depigmentation of sections of skin. It occurs when melanocytes, the cells responsible for skin pigmentation, die or are unable to function. Could be localized or generalized.

We will discuss 5 major endocrine dysfunctions caused by autoimmunity

1- Type 1 Diabetes mellitus (T1DM)

PANCREASE:

The autoimmune diseases of pancreas is an endocrine diseases but, the diseases that involve the secretion of pancreatic content into the gut they are an exocrine diseases.



General info: Pancreas is both an endocrine and exocrine gland.

With 3 types of cells in the endocrine part,

1-beta for insulin,

2-alpha for glucagon

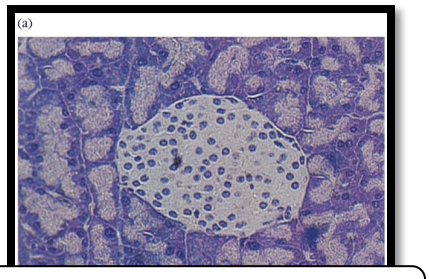
3-delta for somatostatins

Type 1 → (autoimmune)there will be a **destruction of B cell** which will lead to **absence of insulin** the blood.

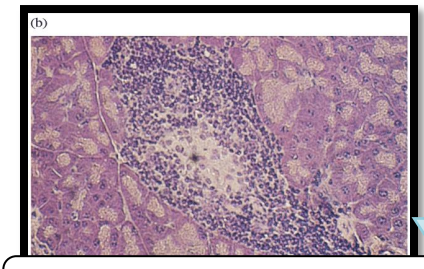
Type 2 → (metabolic) **B cell are normal** and **insulin production are normal** but not effective because there is a problem with the receptors or resistance to insulin

Normally we will find MHC I on all nucleated cell of the body and MHC II only on the surface of APC (antigen presenting cell)

Pancreatic β cells express abnormally high levels of MHC I and MHC II



Normal Pancreas



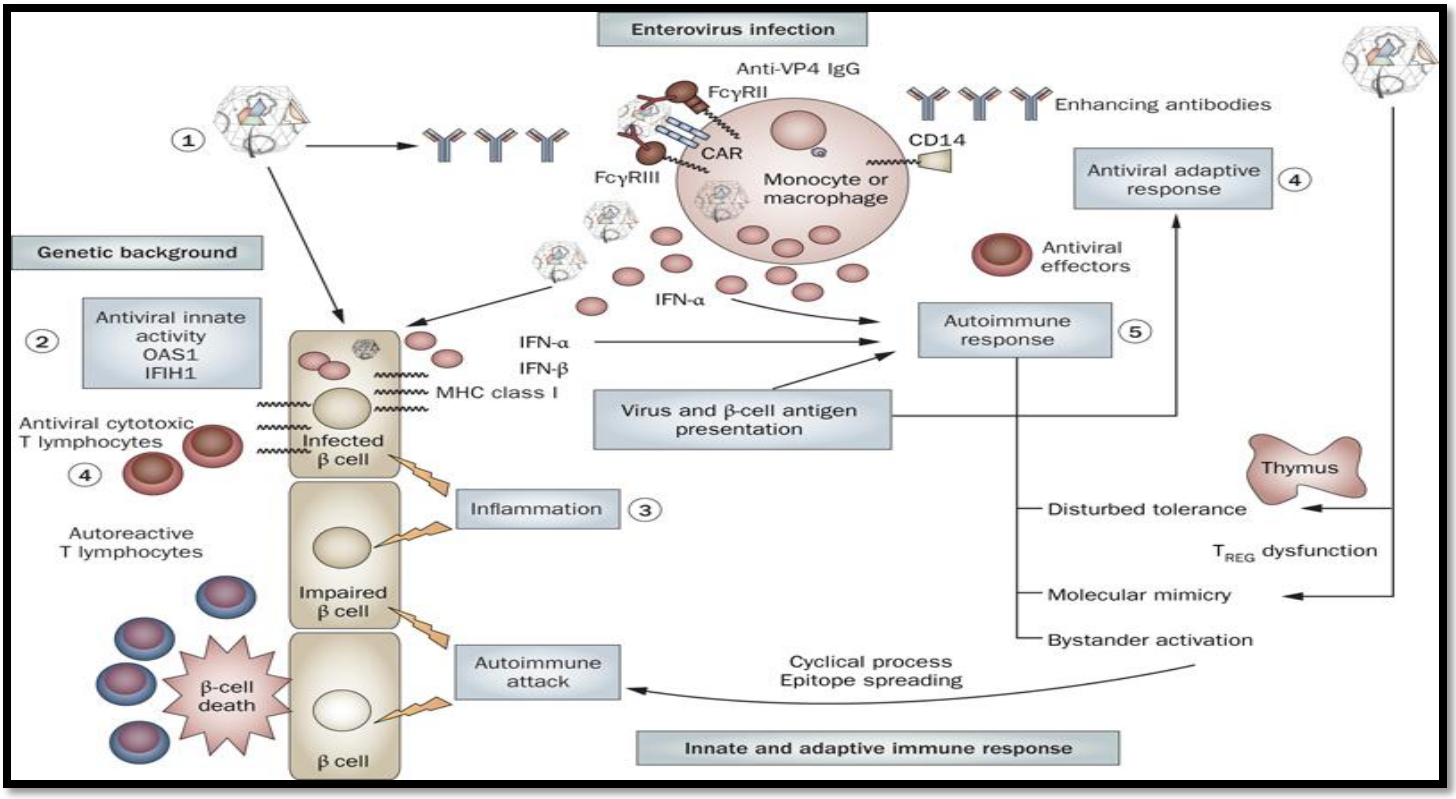
Pancreas with Insulitis

Abnormal

MHC I → If there is an increase in the expression of MHC1 on the cell surface the cells become targets for the immune system.

MHC II → Inappropriate expression of MHC2 on the Bata cells(in case of DM) will lead to the presentation of the beta Ag to the immune system and therefore becoming a target for it.

Normally, the APC have defense mechanisms to withstand the immune system's attack, whereas the beta cells lack these leading to their death



Most common cause of increased MHC expression on the cells is viral infections.

Mechanism:

When the viruses infect the cells, naturally the cells will release INF gamma. ➔INF gamma enhances the presents of MHC1 on the cell (to a higher level) and MHC2 if it is not present

MHC2 will be enhanced on the beta cells (they act as APC), which start to present their own Ag causing autoimmunity and viral Ag to MHC1 becoming targets for CD8 T cells which will destroy them.

MHC1: presents viral Ag and tumor Ag to CD8 T calls.

MHC2: presents the Ag to CD4 T cells leading to chronic inflammmation

So there are 2 ways that the pancreatic B cell can be damage:

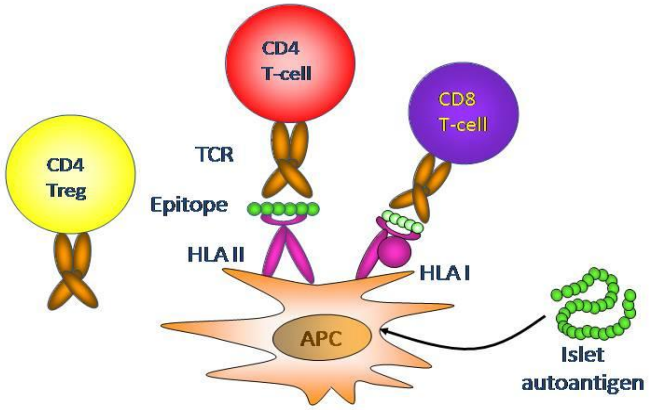
1-when there is an expression of MHC I on the pancreatic B cell, it will be presented as an antigen to CD8 “cytotoxic T cell” which eventually will lead to destruction of Pancreatic B cell.

2-when there is an expression of MHC II on the Pancreatic B cell it will be recognized by CD4 “T helper cell” which will activate the autoreactive cell to attack the pancreatic B cell as a foreign antigen to destroy it.

Type 1 diabetes

HLA = MHC

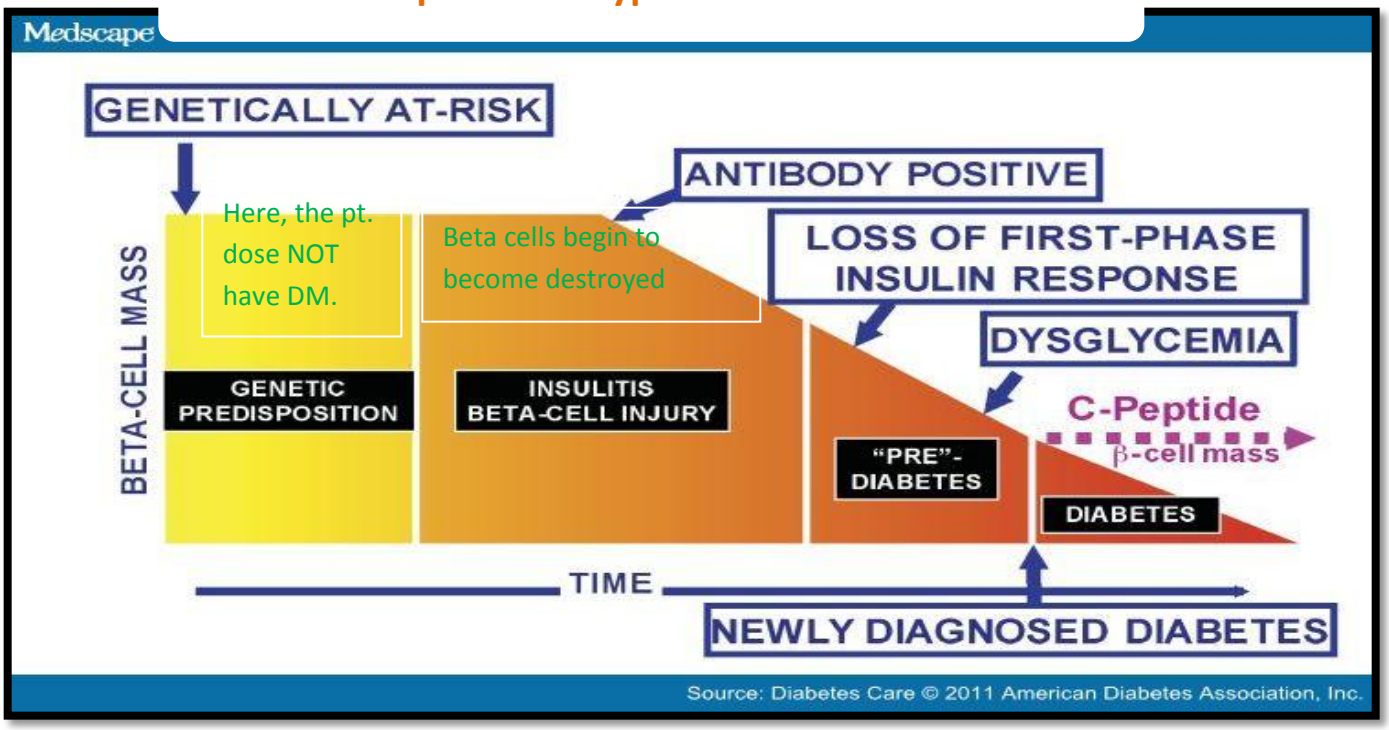
- is**T cell mediated**
- Infiltrating **CD4**+, **CD8**+ **T cells**
- Anti-T cell therapies are effective
- Islet cell autoantibodies ≠disease



CD4 T regulatory cell also called suppressor cell → there function is to suppress the development of autoimmunity. In type 1 diabetes something happen(unknown) to these cells will lead to decrease number of these cells so autoimmunity will develop.

CD8 cells recognize the viral Ag leading to destruction of the APC.

Development of Type I diabetes mellitus



Beta cell mass = number of beta cell .

First phase insulin response, after the meal insulin will be produced in high amounts to digest the carbohydrates preventing an increase in the blood sugar levels.

C-peptide can be detected in blood. If it is positive this means there is an insulin production but, if it's negative this means there is not insulin production.

Kids are more prone then others to get type 1

Predisposition

- **Genetic (HLA DRB, DQA, DQB)**
- **Viral infections**
- Stress
- Environmental exposure - exposure to certain chemicals or drugs

This means that the type 1 diabetes could be caused byenvironmental factor and genetic factor

- 10% chance of inheriting if first degree relative has diabetes
- **Most likely to be inherited from father**

Type I Diabetes

- Four auto-antibodies are markers of beta cell autoimmunity in type 1 diabetes:
  - **Islet Cell Antibodies (ICA)**, against cytoplasmic proteins in the beta cell found in 75-90% patients
  - Antibodies to **Glutamic Acid Decarboxylase 65** (GAD65) in 80% of patients
  - **Insulin Auto-antibodies (IAA)** is the first marker found in 70% of children at the time of diagnosis
  - **IA-2A**, (Insulinoma associated 2 auto-antibodies) to **protein tyrosine phosphatase**found in 54-75% of patients

Limitations of these AB's

- Auto-antibodies may disappear months or years later without the development of diabetes for unknown reasons (so if a person is (+) for an AB, can't say that they have D.M straight away)
- Since insulin-treated patients develop insulin antibodies, **analysis of IAA is not useful in insulin-treated patients**
- **Antibodies may be transferred trans-placentally to infants of type 1 diabetic mothers** so caution must be used for interpretation

The immune system normally knows the insulin Ag and does not react to it.

Anti-insulin antibodies

- Anti-insulin antibodies either of IgG and/or IgM class against insulin are elevated and this may make insulin less effective or neutralize it

IgG: is the **most common** type of anti-insulin antibody → Can cross placenta

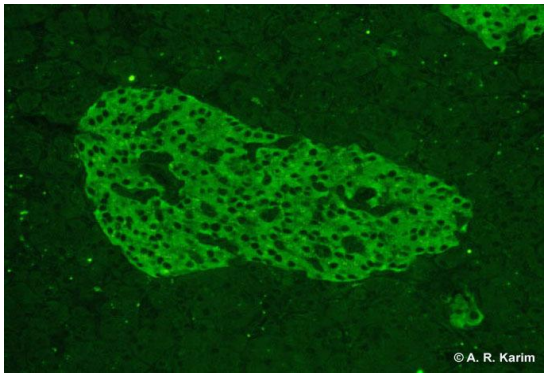
IgM: may cause **insulin resistance**

IgE: may be responsible for **allergic reactions**

Islet cell antibody (Immunofluorescence)

Islet cell normally not seen in immunofluorescence

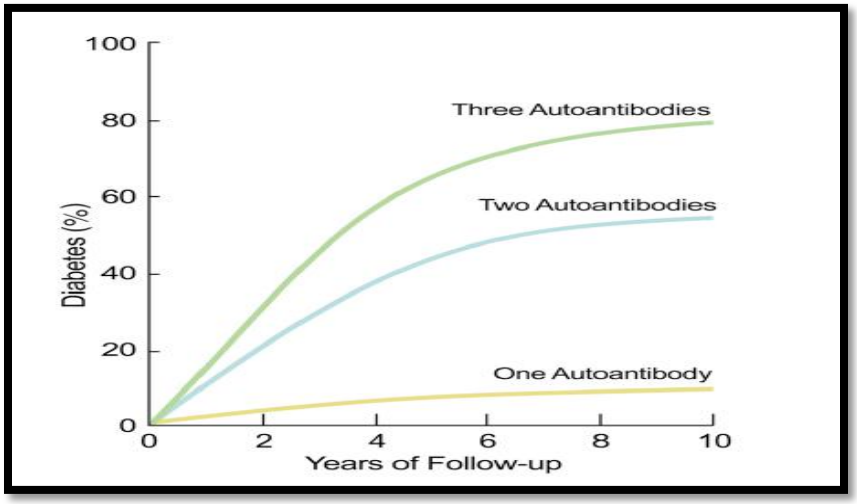
Section of the pancreas stained with IF, which here is positive.



Prediction of TIDM

The presence of AB in the serum of a patient will help in determining the chances and the duration till they are diagnosed with diabetes.

Increased number of AB, increases the chances

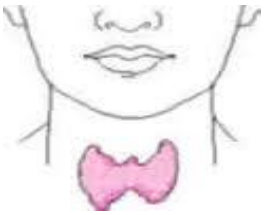


Disease associations

About 10% patients with Type 1 diabetes are prone to other autoimmune disorders such as:

- Addison's disease
- Pernicious anemia
- Graves' disease
- Hashimoto's thyroiditis

2-Thyroid autoimmunity



Hypothyroidism

- Hashimoto's disease
- Atrophic thyroiditis

Hyperthyroidism

- Graves' disease **o**nly time when there is autoimmunity leading to increased function

A-Chronic Lymphocytic Thyroiditis (Hashimoto's Thyroiditis)

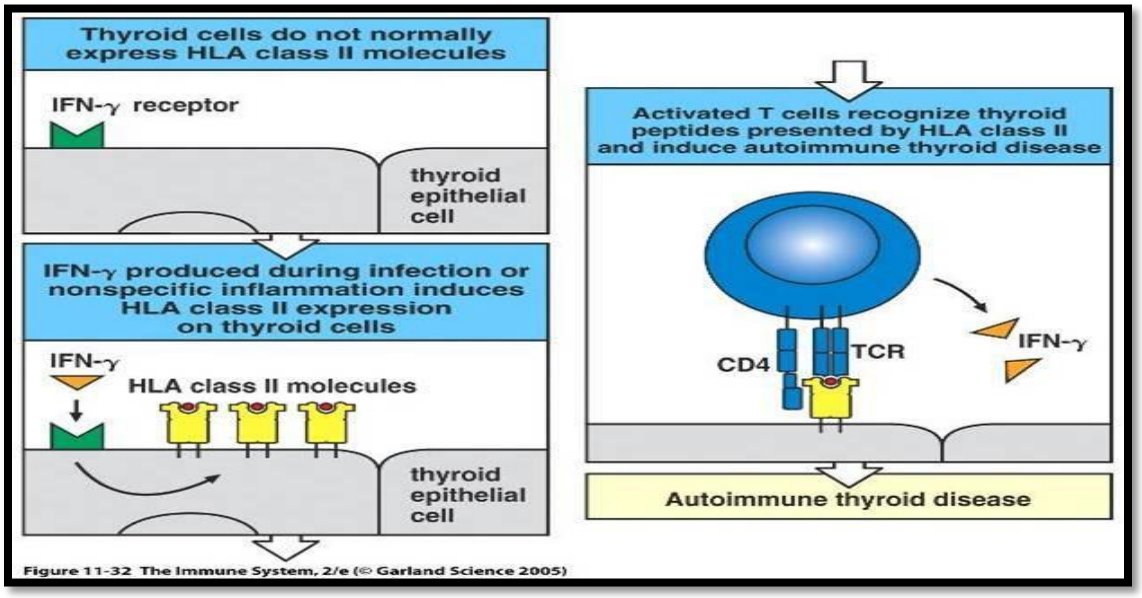
- Male: Female ratio is 1:33 women more effected
- **Associated with HLA-B8**
- Symptoms of hypothyroidism
    - Fatigue
    - Increased sensitivity to cold
    - Unexplained weight gain
    - Dry skin
    - Hoarseness
    - Puffy face
    - Thinning hair

- Frequently affects middle-aged women
- Individuals produce auto-antibodies and sensitized TH_1 cells specific for thyroid antigens. Mostly cell mediated immunity (CD4 and CD8 cells. CD8 will kill the APC)
- It is a **delayed type of hypersensitivity response** and is characterized by:
    - An intense infiltration of the thyroid gland by lymphocytes, macrophages, and plasma cells, which form lymphocytic follicles and germinal centers

Hashimoto's-*Pathogenesis*

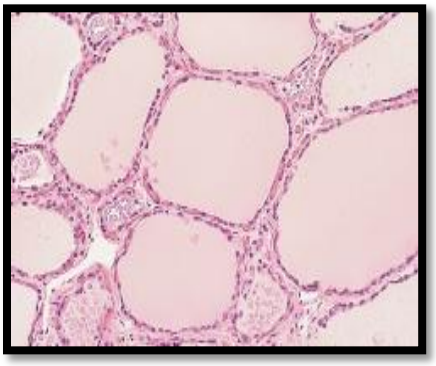
- Sensitization of **autoreactive CD4+ T-helper cells** to thyroid antigens appears to be the initiating event.
- The thyrocytes may be destroyed by:
  - ***CD8+ cytotoxic T cell-mediated cell death*:**CD8+ cytotoxic T cells may cause thyrocyte destruction by either:
    - Perforin/granzyme granules
    - Engagement of death receptors (Fas) on the target cell death of cell by apoptosis
    -
  - ***Cytokine-mediated cell death*:** CD4+ T cells produce inflammatory cytokines such as IFN-γ followed by recruitment and activation of macrophages and damage to follicles.
  - **Binding of antithyroid antibodies:** followed by antibody-dependent cell-mediated cytotoxicity (ADCC)

Same concept as DM

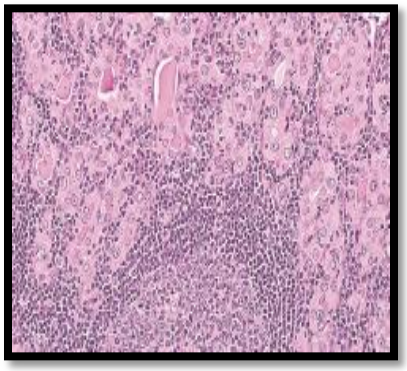


Hashimoto's Thyroiditis

Lymphocytic infiltrate in the thyroid gland, with lymphoid follicle formation and fibrosis



Normal thyroid histology



Hashimoto's throiditis with intense cellular

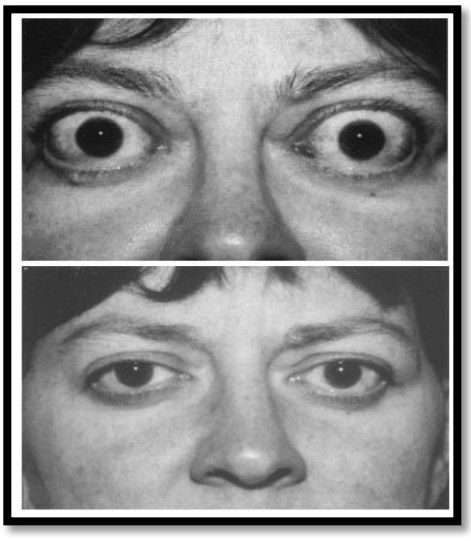
Hashimotos' thyroiditis

- The inflammatory response causes:
- A goiter, or visible enlargement of the thyroid gland
- Antibodies are formed to a number of thyroid proteins, including:
  - **Thyroglobulin**
  - **Thyroid peroxidase (it also called anti-microsomal antibody)** → More common

(both are involved in production of thyroid hormone)

Typical case, increase TSH and a decrease in T4

B- Graves' disease

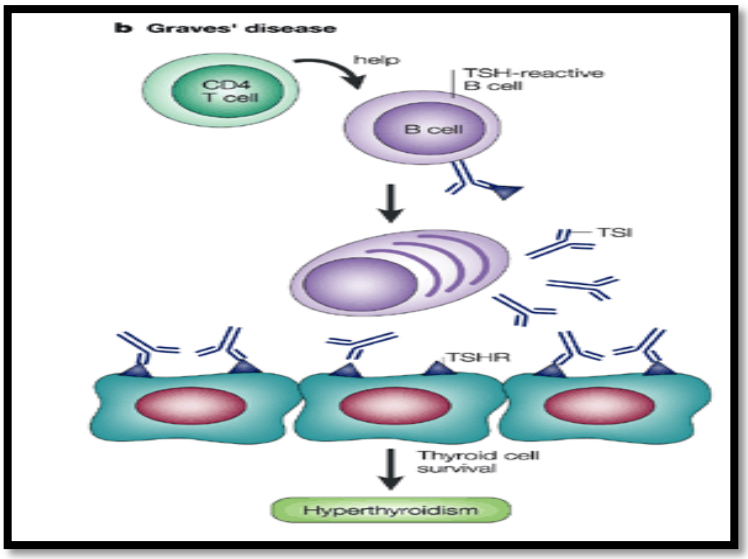


- Clinical Features:
  - Agitation
  - Sleep disturbance
  - Sweating
  - Palpitations

- Muscle weakness
- Weight loss despite increased appetite
- Goiter
- Tremor
- Ophthalmopathy (Exopthalmos)

- Less common than Hashimoto's disease
- Male: Female ratio 1:7
- **Associated with HLA-B8**
- Characterized by production of stimulating **antibodies against TSH receptors**

Graves' Disease (pathogenesis)



The production of antibodies in Graves' Disease is thought to arise by **activation of CD4+ T-cells**

Followed by B-cell recruitment into the thyroid

These B-cells produce antibodies specific to the thyroid antigens

The thyrotropin receptor (Thyroid Stimulating Hormone (TSH) receptor) is the antigen for TSH receptor antibodies (TRAbs)

There are three types of TSH receptor antibodies:

- Activating antibodies (associated with hyperthyroidism)
- Blocking antibodies (associated with thyroiditis)
- Neutral antibodies (no effect on receptor)
-

Thyroid Stimulating Immunoglobulin (TSH receptor antibodies) majority 75%

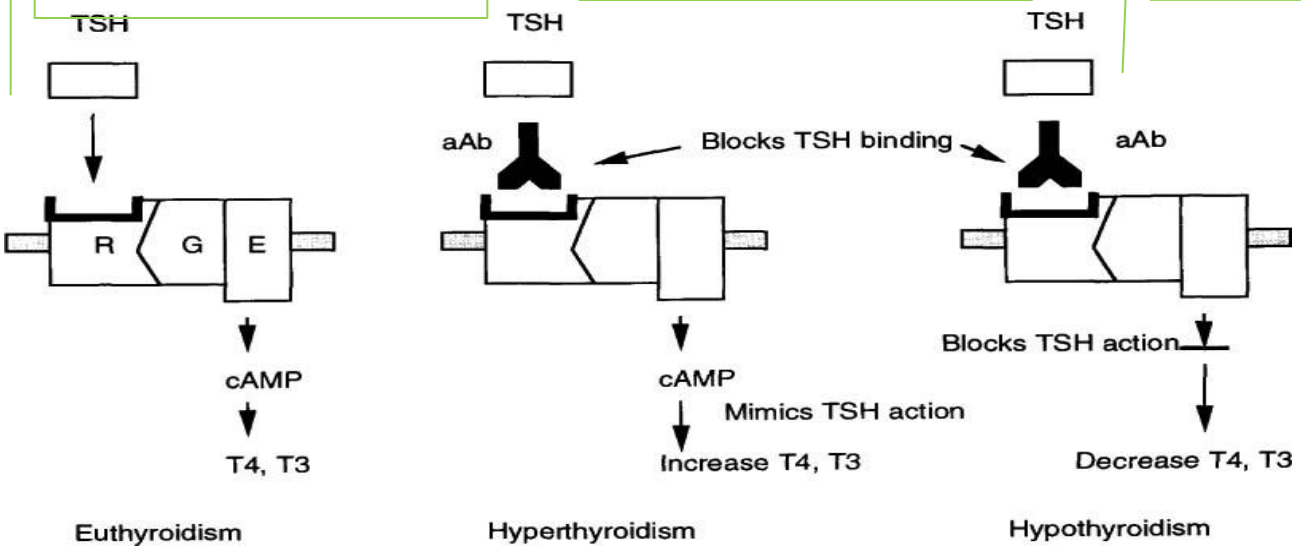
Not associate with graves disease

Normally. TSH binds to its receptor activating adynylcylase which will increase conversion of ATP to cAMP and further formation of T4 and T3.

Here, the negative feedback inhibition is active

In Graves disease, there is TSH receptor AB, which binds to the receptor instead of the hormone. This will lead to an increased thyroid activity and loss of feedback inhibition

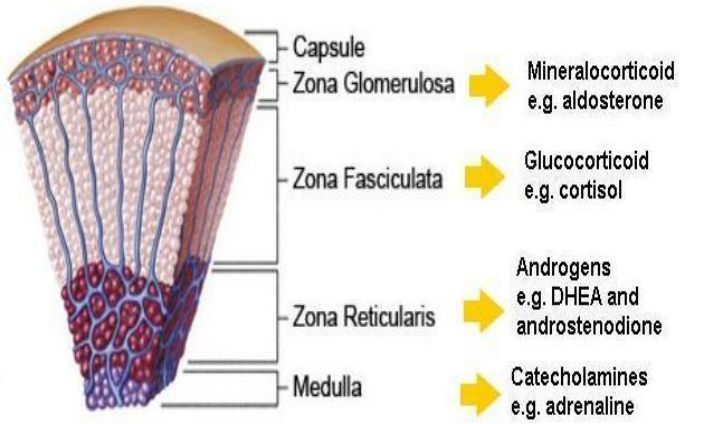
In case of a blocking AB, it will block the action of TSH and lead to hypothyroidism.



3Addison's disease (Primary adrenal insufficiency)

Effects/ destruction of the cortex (so both corticosteroids and aldostrone will be effected)

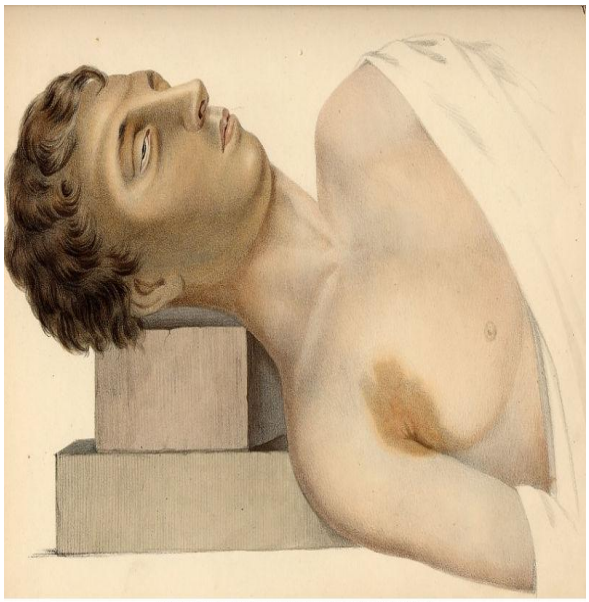
- Female: Male ratio: 4:1
- Susceptibility genes:
  - **HLA-DR3 and/or DR4**



Primary adrenal insufficiency: Symptoms & Physical findings

- Weakness
- Weight loss * hypotention
- Poor appetite * weak pulse
- Confusion * shock
- Hyper-pigmentation

Aldostronehas two functions. Increase blood pressure and water retention



Hardin Library for the Health Sciences. John Martin Rare Book Room

Autoimmune Adrenocortical Failure, or Addison's disease

- It develops as a consequence of **autoimmune destruction of steroid-producing cells** in the adrenal gland
- **The major auto-antigen is 21-hydroxylase**
  - An enzyme involved in the biosynthesis of cortisol and aldosterone in the adrenal cortex

Autoimmune Adrenalitis

1- ***Humoral Immunity:***(AB)
   - Autoimmune adrenalitis is characterized by the presence of serum antibodies against
     - **21-hydroxylase**
     - **17-alpha-hydroxylase**
   - The serum concentration of auto-antibodies, specifically against 21-hydroxylase correlates strongly with the degree of adrenal dysfunction
   - Adrenal insufficiency becomes clinically evident only after at least 90 percent of the cortex has been destroyed

2- ***Cellular Immunity*:**(CD 8 / CD 4)

- The presence of **lymphocytic infiltration** in the adrenal glands
- A **Th1 response** characterized by the production of **Interferon-gamma**
- An antigen-specific T helper cell-driven process with cytotoxic T lymphocytes and activated macrophages mediate the destruction of the adrenal cortex

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4- Gonads:overies and testicals may be targeted by the immune system

Autoimmune oophoritis

(Inflammation of the ovaries)

Autoimmune orchitis:

Testicular pain involving swelling, inflammation and infection

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5- Pituitary gland

Lymphocytic hypophysitis: Inflammation of the gland (autoimmune) resulting in decreased production of one or more hormones by the pituitary gland

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Lecture Objectives:

- To understand that immune system can target either single or multiple organs
- To know that autoimmunity against endocrine glands can cause endocrine dysfunctionDysfunction means destruction of the gland and loss of function, this is the usual immune action, except in the thyroid it may lead to hyper-function
- To understand various cellular and humoral auto-immune mechanisms involved in different endocrine disorders
- To know about the endocrine disease associations

Take home message:

- Either single or more than one endocrine glands may be targeted by immune system in a particular patient
- Immunological damage to endocrine glands is mediated by autoimmune reactions
- Endocrine dysfunction associated with immunological injury in majority of cases is due to end organ failure except in Graves's disease.
- Patients suffering from a particular immune mediated endocrine disorder frequently harbor antibodies against other endocrine glands.

Qs

1. Which one of the following condition mediates damage in pancreatic islet beta cells in insulin dependent diabetes mellitus (IDDM)?

A. NK-cell

B. T-cell

C. Complement

D. Plasma cell

2. Which one of the following autoantigens is the major target of autoimmune damage in Addison's disease?

A. 21-hydroxylasea

B. Glutamic acid decarboxylase

C. Peroxidase

D. Adenylcyclase

3. Which one of the following antibodies is commonly present in hashimmoto's thyroiditis?

A. anti-microsomal (thyroid peroxidase)

B. anti-mitochondrial

C. anti-ribonucleoprotein

D. anti-double strand DNA