Lecture (1)

The Immune System and Endocrine Disorders

Objectives:

- To understand the mechanisms involved in immunological damage to the endocrine glands.
- To know about various endocrine disorders such as Graves' disease, hashimoto's thyroiditis, type I diabetes and Addison's disease resulting from autoimmunity.
- To describe the association of certain auto-antibodies with regards to their pathogenic and diagnostic importance.

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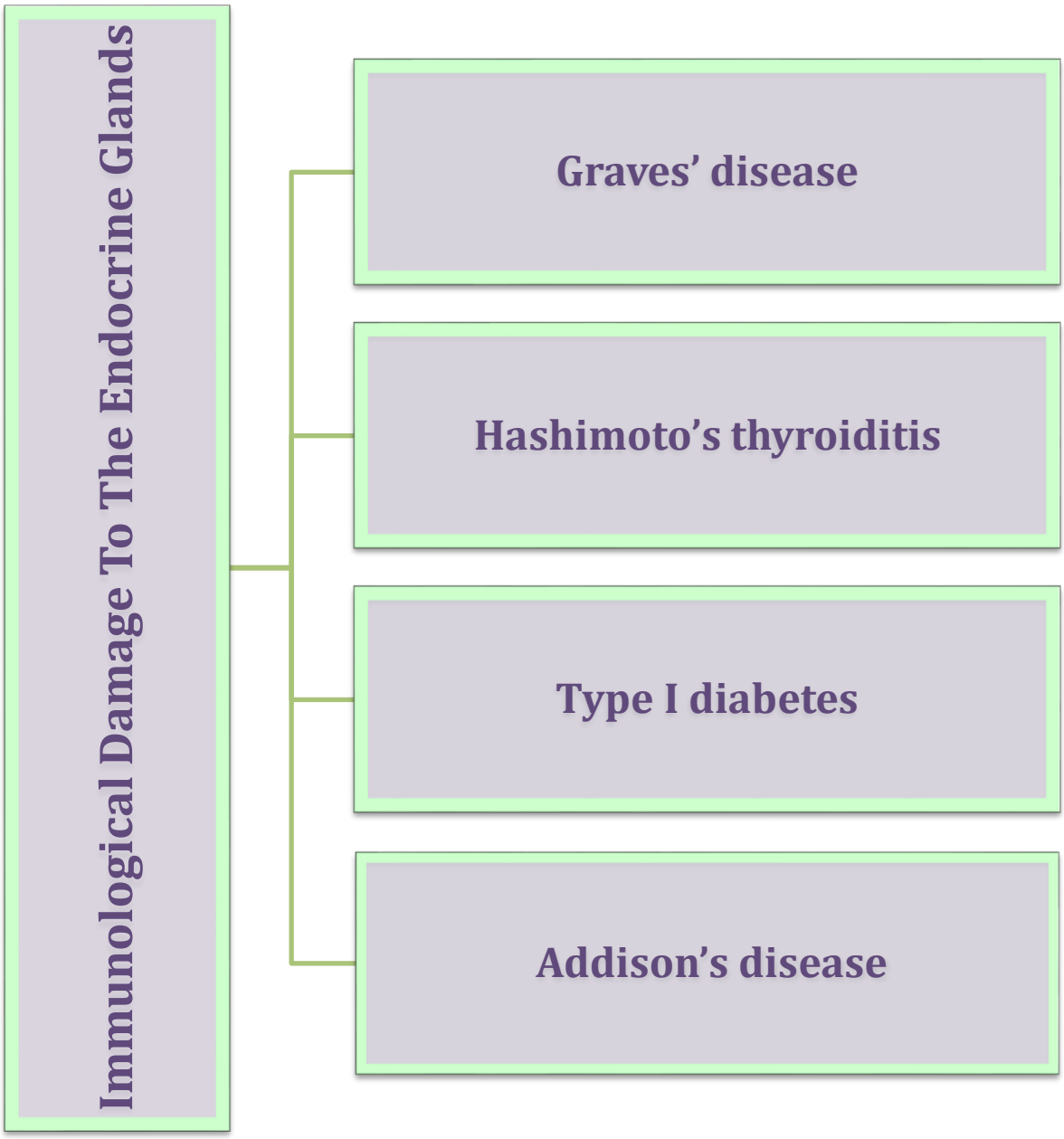
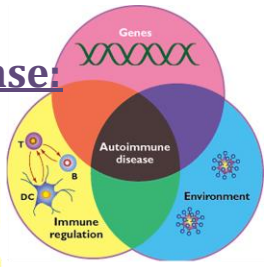
#Slides #Important #Doctor's Notes #Extra info


Immunological Damage To The Endocrine Glands
Graves' disease
Hashimoto's thyroiditis
Type I diabetes
Addison's disease

Three factors that may contribute to Autoimmune disease:

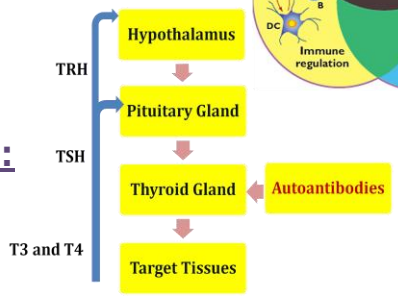
1) 1.Genes
2) 2.Immune regulation
3) Environment ex: Food or a viral Antigen

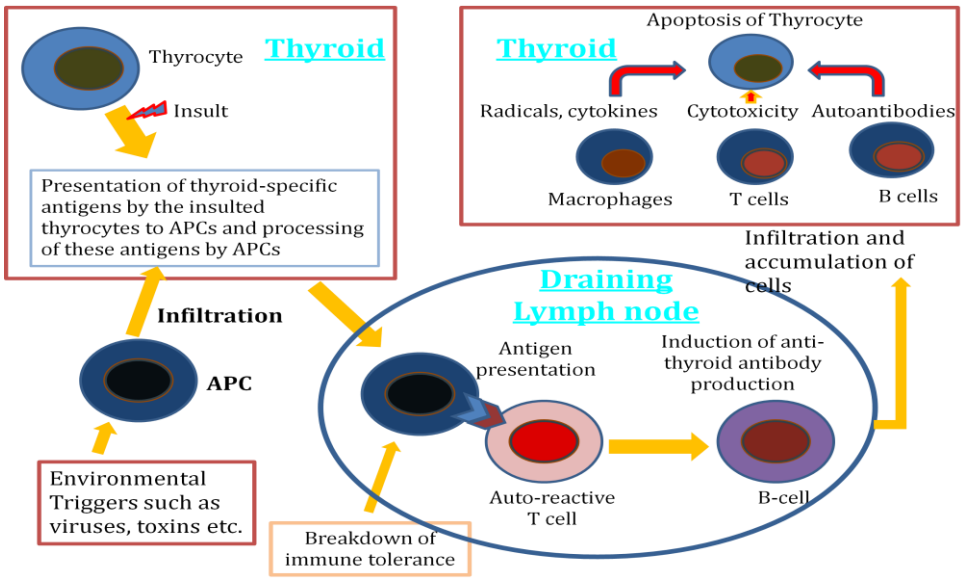


Autoimmune diseases of the Thyroid gland:

1) 1.Graves' disease
2) 2.Hashimoto's thyroditis

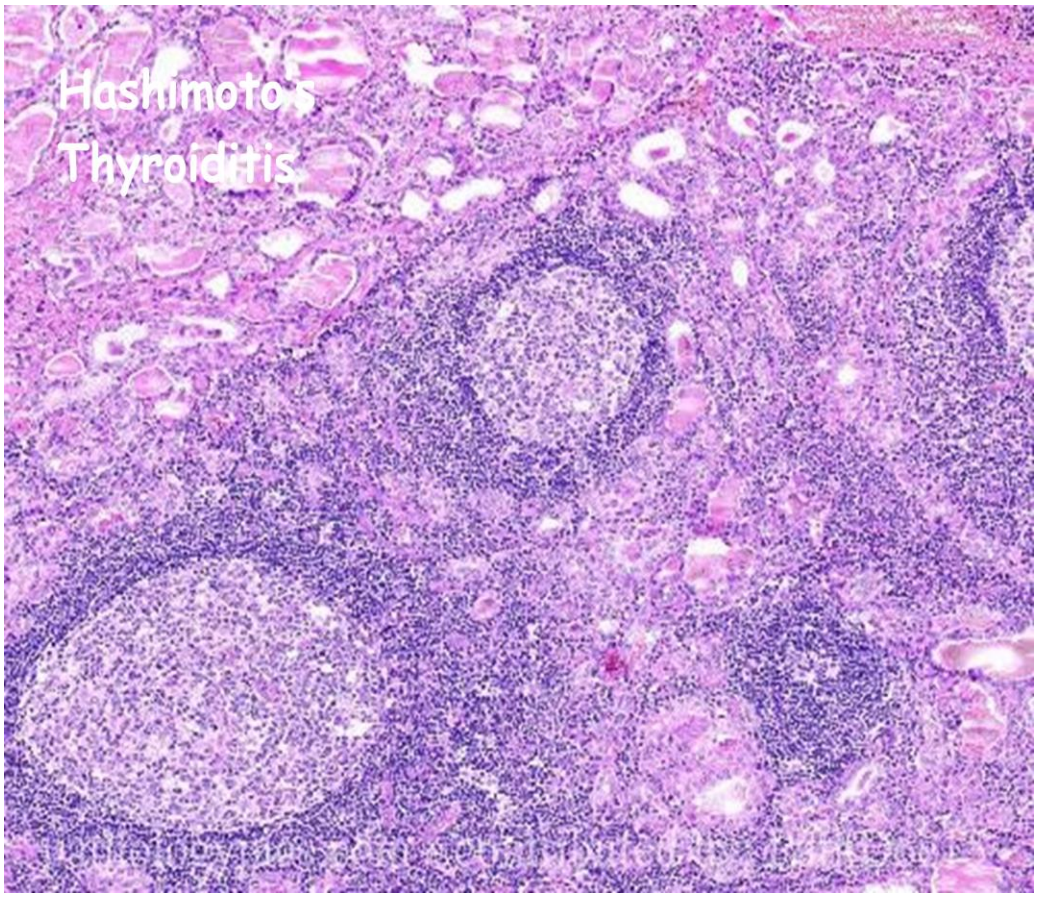
" We can see evidence of cell mediated and humoral immunity"



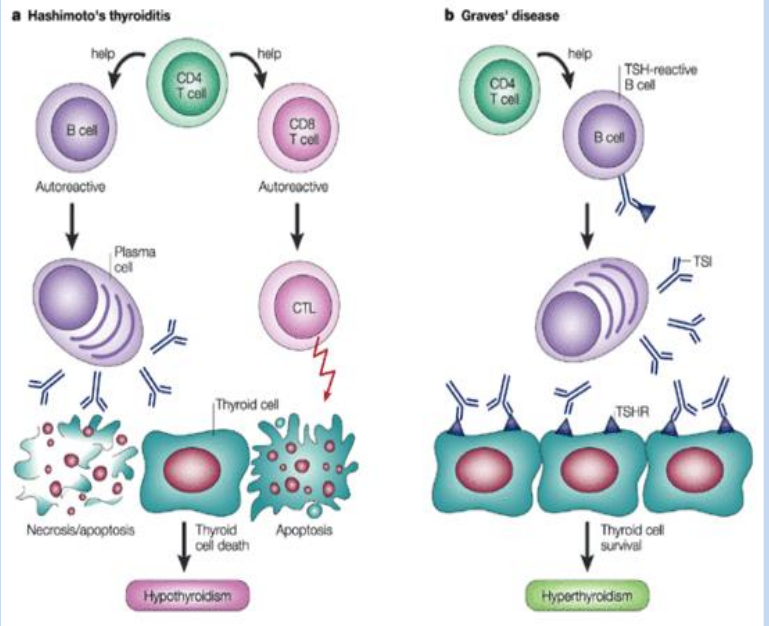


- It is believed that non specific injury will release its **Antigen** and they are taken up by the **APC** "antigen presenting cells".
- Those **Ags** will most likely go to the nearest lymph node where it will be presented to different types of cells
- **Theories:**
  - **Auto-reactive T-cells** keep the cells into check like a police stop. When they see a foreign body they will attack it.
  - **Ag** is Presented to T-cell"CD-4" will either be cell mediated by T-helper1,or Humoral immunity by T-helper2. At the same time T-cells will mediate B-cells forming Antibodies.

The result: Activation of Macrophages, Cytotoxins, Antibodies destroying the thyrocytes.

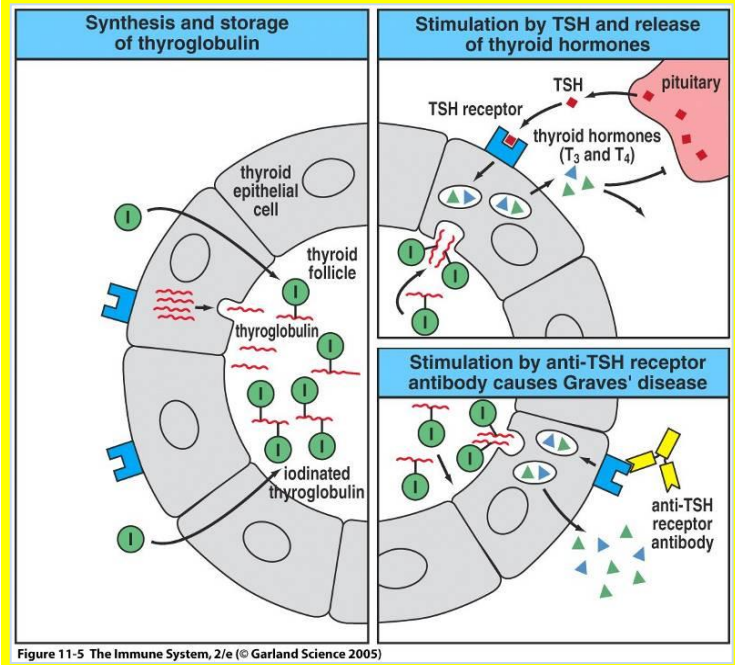


Cell mediated causing diffuse parenchymal infiltration by **lymphocytes**.



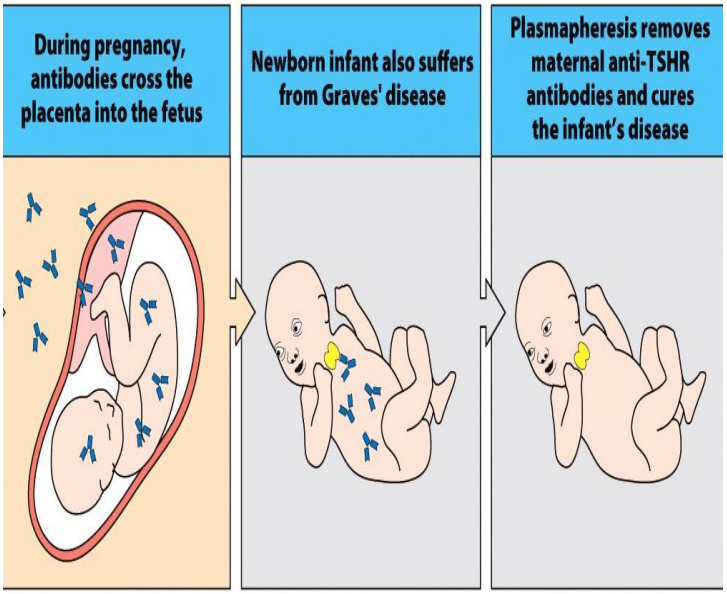
A: Hashimoto's thyroditis can cause both Humoral and cell- mediated immunity activating B and T-helper cells. Causing cell destruction leading to **Hypothyroidism**

B: Graves' disease activates B-cells that will induce Thyroid stimulating hormone receptor antibody "Thyroid stimulating Immunoglobulin" binding to the TSH receptor in the thyrocyte causing hyperactivity leading to **Hyperthyroidism**



This image shows how the stimulating antibodies act on the thyroid cells as shown in the box bellow similarly as the TSH normally does, by activating T3 and T4. The Anti-TSH receptor antibody will stay there for a long time stimulating the hormone and also occupying the receptor so TSH receptor won't be able to bind normally. This will cause TSH accumulation outside the cell.

Mother with Graves' disease makes thyroid stimulating hormone receptor antibodies

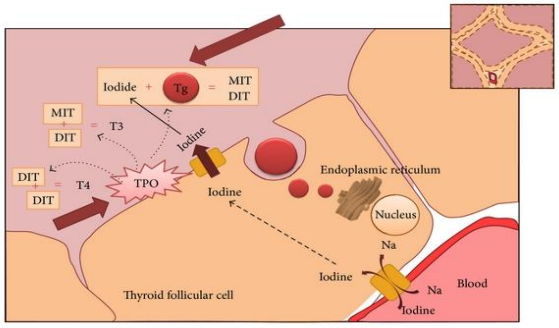


- Here a mother with Graves' disease carrying IgG "the only immunoglobulin that can cross the placenta" will stimulate thyrotoxicosis in the new born. In the first three to six months the baby will suffer from thyrotoxicosis knowing that the T half of IgG in 27days. It will disappear after that.
- So we have to evaluate the child after birth.
- Treatment will be by controlling the symptoms and by Plasmapheresis (Removing plasma "that contains IgG" from the blood then returning the blood into the baby without the plasma.

In Hashimoto's antibodies will block the receptor which won't allow TSH to function causing Hypothyroidism.

We see:

- Anti- Thyroid Microsomal antibody (Against the Microsomes "found normally in the thyroid follicles, when the thyroid cells are damaged the body produces antibodies to microsomes).
  - **<u>Other names include:</u>**
    A. Thyroid anti-microsomal antibody
    B. Anti-microsomal antibody
    C. Microsomal antibody
    D. Thyroid proxidase antibody (TPOAb)
- Anti-thyroglobulin antibody (less commonly elevated than Anti-Microsomal Ab).



- ✓ TPO (Peroxidase): is a membrane bound enzyme that synthesis the Thyroid hormones.
- ✓ When there are Antibodies against TPO it will inhibit its activity.

<u>TPO</u> can be detected in different situations:

- More than 90% in Hashimoto's thyroditis
- 50% in Graves' disease (Stimulated by Antigen- antibody reaction that will cause hyper functioning and cell destruction).
- Less frequently in patients with other thyroid diseases
- 5-10% in Normal indiviuals (They will either get thyroitoxicosis later on, be perfectly normal, or have another autoimmune disease like Diabetes)

Low titers may also be found in 5-10 percent of normal individuals

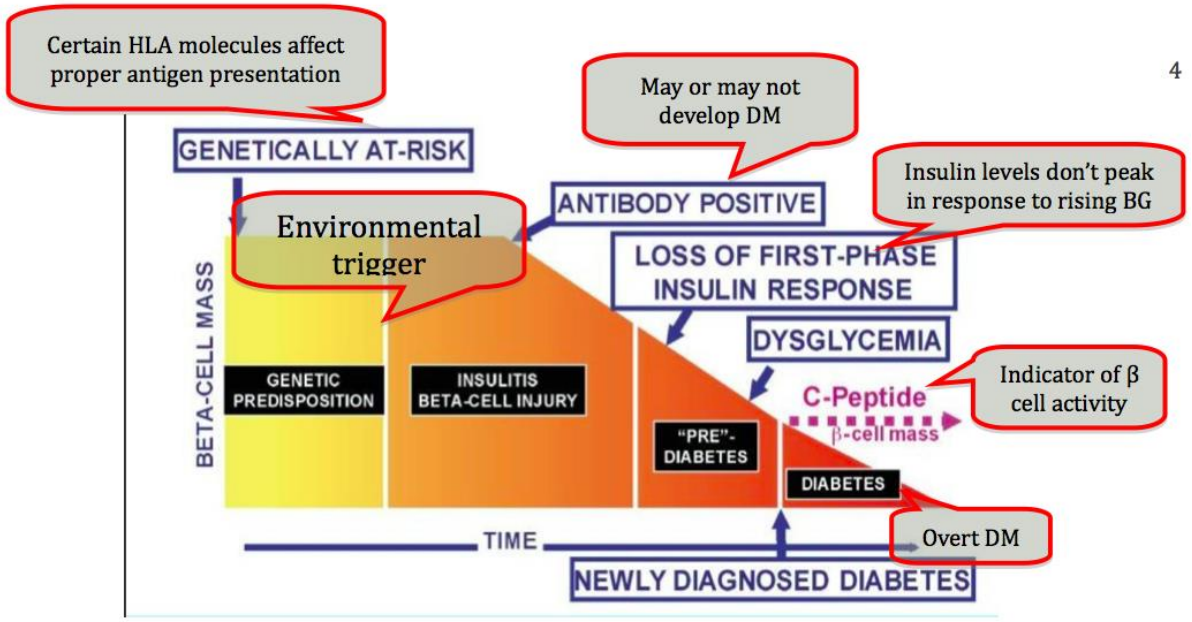
(A)Definition:

- Autoimmune (immunological) destruction of beta cells in the pancreas which secrete insulin. Requires insulin administration for controlling high blood glucose usually in children while type II is in 40+ y/o.
- Recent evidence suggests that both share the same process. It's just the matter of the intensity of the destruction.

(B)Predisposition:

- Genetic (HLA DRB, DQA, DQB). HLA class II is concerned with antigen presentation.
  - 10% chance of inheriting if first degree relative has diabetes.
  - Most likely to be inherited from father.
- Viral infections: Infection introduces a viral protein that resembles a beta cell protein. Cross-reacting T-cells and antibodies because of molecular mimicry attack beta cell proteins and viruses such as mumps, measles, Coxsackie B.
- Stress
- Enviromental exposure (certain chemicals or drugs.)
  - Cow's milk: Certain protein which may trigger attack on beta cells (molecular mimicry).

Development of type I DM



(B)Antibodies:

- Four auto-antibodies are markers of beta cell autoimmunity in type 1 diabetes:

Antibody	Percentage	Directed against	Other
Islet cell antibodies (ICA)	75-90%	Cytoplasmic proteins	
Antibodies to GADS65	80%	Glutamic acid carboxylase 65	
Insulin autoantibodies (IAA)	70%		First marker found in children at time of diagnosis
IA/2A	54-75%	Protein tyrosine phosphatase	

- Type 1 diabetes may be diagnosed by the presence of one or more auto-antibodies
  - • People who screen positive for one or more auto-antibodies may ***not*** necessarily develop diabetes.
  - • Risk of having type 1 diabetes is proportional to titer of antibodies.

Differential diagnosis :

- Type 1 diabetes may be diagnosed by the presence of one or more auto-antibodies
- People who screen positive for one or more auto-antibodies may ***not*** necessarily develop diabetes
- Risk of having type 1 diabetes is proportional to titer of antibodies.
- High titers/more than one autoantibody increase the likelihood of developing T1DM.

Interpretation :

- Antibodies may be present several years before a patient develops hyperglycemia.
- Presence of auto-antibodies impairs insulin response. Have abnormal glucose tolerance.

Limitations:

- Auto-antibodies may disappear months or years later without the development of diabetes.
- Since insulin-treated patients develop insulin antibodies, analysis of IAA is not useful in insulin-treated patients. Anti-insulin antibodies detected in serum of those treated with exogenous insulin, it's not their own protein and it will trigger production of antibodies.
- Antibodies may be transferred trans-placentally to infants of type 1 diabetic mothers so caution must be used for interpretation. Mother who has IDDM may transfer antibodies to newborn which may hamper the function of insulin.

Anti-insulin antibodies:

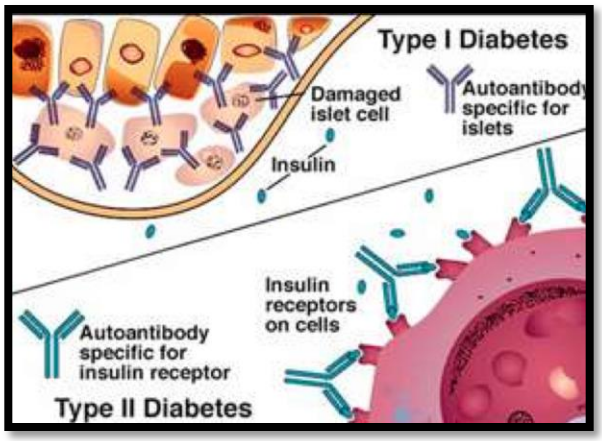
- Anti-insulin antibodies either of IgG and/or IgM class against insulin are elevated and this may make insulin less effective or neutralize it.
  IgG: is the *most common* type of anti-insulin antibody.
  IgM: may cause insulin *resistance.*
  IgE: may be responsible for *allergic* reactions in those being treated with exogenous insulin.

Disease associations:

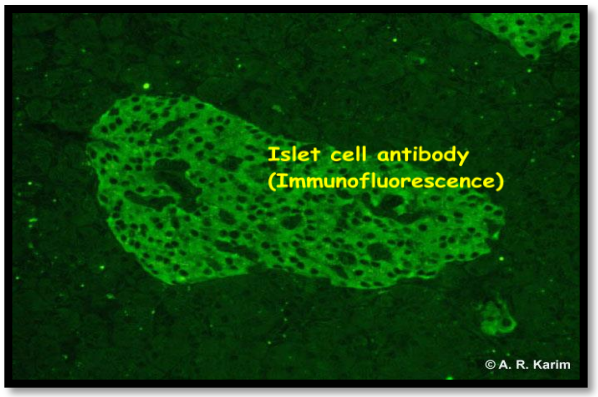
About 10% patients with Type 1 diabetes are prone to other autoimmune disorders such as:

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

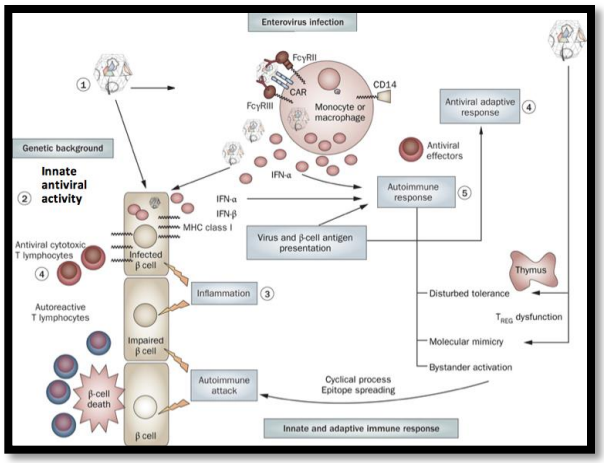
Autoimmune diseases travel in clusters so in a T1DM you might see anti-TPO or thyroglobulin antibodies. One very common disease that occurs simultaneously is celiac disease.



T1DM: Antibodies are directed against beta cells and insulin.
T2DM: Antibodies are occupying receptors and preventing insulin from binding.



Antibodies binding across the islets signifying inflammation and subsequent release of antigens leading to autoimmunity.



Virus infected cells release INF (antiviral) which will enhance *MHC I presentation* and *inappropriate expression of MHC II* on Beta cells - which normally don't express MHC II molecules- will act as an APC and present their own antigens leading to *cell mediated* autoimmunity by becoming a target to autoreactive T-cells.

(III)Adrenal glands

Autoimmune adrenocortical failure or Addison's disease:

- It develops as a consequence of autoimmune destruction of steroid-producing cells in the adrenal gland
- 75 to 80% of all cases of adrenal insufficiency or Addison's disease are of autoimmune origin with circulating anti-adrenal antibodies
- The damage is probably mediated by T cells and the role of antibodies is unclear.

Adrenal antibodies:

- Adrenal antibodies are also known as adrenocorticol antibodies (ACA)
- Antibody to **21-Hydroxylase** an enzyme involved in biosynthesis of cortisol and aldosterone is the best marker of autoimmune Addison's disease,
- Other antibodies rarely tested are:
  - 17 alpha hydroxylase
  - Cytochrome P450

Thyroid gland

- Graves' disease is caused by stimulating antibodies.
- Graves' disease activates B-cells that will induce Thyroid stimulating Immunoglobulin causing hyperactivity leading to Hyperthyroidism.
- Hashimotos thyroiditis is associated with tissue damage mediated by proinflammatory cells and antibodies directed to self antigens in thyroid gland.
- Hashimoto's thyroditis can cause both Humoral and cell- mediated immunity activating B and T-helper cells. Causing cell destruction leading to Hypothyroidism
- 90% of patients with Hashimoto's thyroiditis have thyroglobulin or thyroid microsomal antibodies

Type I diabetes mellitus:

- results from immune mediated destruction of beta cells in pancreas and a number of auto-antibodies can be detected in patients
- Insulin Auto-antibodies (IAA) is the first marker found in 70% of children at the time of diagnosis
- Risk of having type 1 diabetes is proportional to titer of antibodies.

Addison's disease

- In majority of patients with Addison's disease evidence of auto-immunity can be detected by the presence of anti-adrenal antibodies.
- Antibody to 21-Hydroxylase an enzyme involved in biosynthesis of cortisol and aldosterone is the best marker of autoimmune Addison's disease.

Summary from Lippincott's:

Autoimmune pathology may result from:

1. **Humoral associated autoimmune** disease which results from anti-body initiated damage; (hypersensitivity type 2 or type 3)
   For example :
   Hashimoto's thyroiditis: Type 2 hypersensitivity

2. **Cell mediated response** (Type 4 hypersensitivity)
   For example:
   Insulin-dependent diabetes mellitus (type 1.)

Disease	HLA gene	Relative risks
Grave's Disease	DR3	4
Hashimoto's thyroiditis	DR5	3
Type 1 insulin-dependent diabetes mellitus	DR3/DR4 heterozygote	20-25

Q.	A.
1	b
2	d
3	c
4	e
5	b
6	a

1- **If we found an antibody in Graves' how do we demonstrate that it's a stimulating antibody? (Asked by the doctor)**

a. Immunohistopathology
b. Bioassay
c. CBC

2- **A previously healthy 12-yr old female lost 8 pounds over the past several weeks without dieting. Her parents are concerned about her weight loss and believe that she has an eating disorder. The pt. history reveals polydipsia (excessive thirst) and nocturia over the last several weeks. Fasting blood glucose of 460 mg/dl is obtained. (reference range 70 to 100 mg/dl). The pt. diagnosed with an autoimmune disease. Which of the following is most likely diagnosis?**

a. Anorexia nervosa
b. Hyperthyroidism
c. Kidney stone
d. Type 1 diabetes
e. UTI

3- **In the previous Q a defect in which of the following is associated with the pt. condition?**

a. Adipose tissue
b. Kidney tubules
c. Pancreatic B cells
d. Thyroid gland
e. Skeletal muscle

4- **A previously healthy 65-yr-old female presents with complaints of frequent bowel movements, weight loss, and nervousness. Her physical examination was remarkable for slight exophthalmos and atrial fibrillation. Lab finiidings supported a diagnosis of Graves' disease, which of the following organ will be affected by immune reactions?**

a) C.T
b) Joints of L.L
c) Heart valves
d) Kidney
e) Thyroid gland

5- **Graves' disease is an example of which of the following immunologic processes?**

a) Autoimmune disease associated with HLA gene B27
b) Autoimmune disease associated with HLA gene DR3
c) Immune deficiency associated with HLA gene DR2
d) Immune deficiency associated with HLA gene DR4
e) Type 3 hypersensitivity associated with HLA gene Cw6

6- **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

***Bioassay :** Determination of the strength or biological activity of a substance, by comparing its effects on a live animal or an isolated organ preparation with those of a reference standard.

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Best wishes, Immunology team 432.