The role of HDL-associated MPO and PON-1 for coronary artery disease in Hashimoto Thyroiditis

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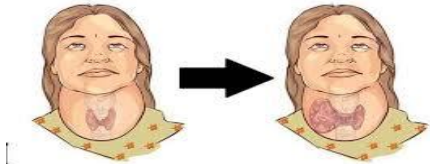
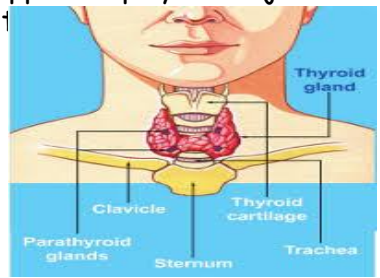
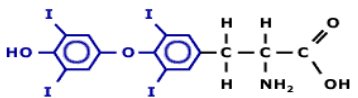


INTRODUCTION

What is thyroid gland?

The thyroid gland is a small butterfly-shaped gland located in the midline of the neck under the cartilage projection called the Adam's apple. It plays a major role in growth and development with the hormones it to weigh only 25 grams.

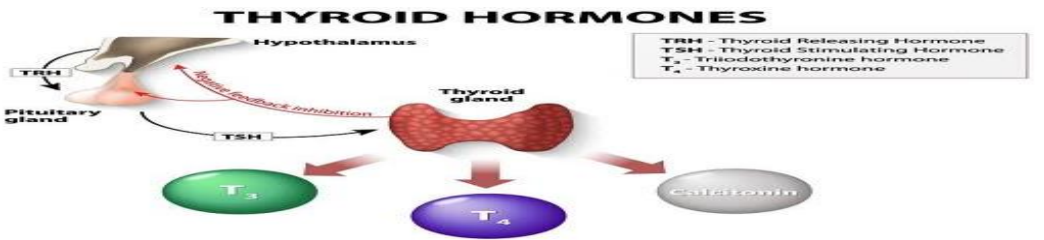




3', 5', 3, 5-tetraiodothyronine
thyroxine, T4

What makes your thyroid gland?

It makes two hormones that are secreted into the blood: thyroxine (T4) and triiodothyronine (T3). These hormones are necessary for all the cells in your body to work normally. The operation of the thyroid gland is controlled by the TSH hormone secreted from a gland called pituitary gland in the brain. When the thyroid hormones in the bloodstream (T4 and T3) decrease, TSH secretion from the pituitary increases and this hormone increases thyroid hormone secretion from the thyroid gland. Conversely, if T4 and T3 increase in circulation, TSH secretion from the pituitary is reduced.



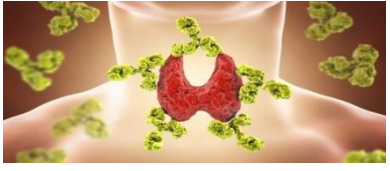
Autoimmune Thyroiditis

Autoimmune Thyroiditis

- An autoimmune disease in which antibodies are produced against 3 major autoantigens in the thyroid gland:
  - Thyroglobulin (Tg)
  - Thyroid peroxidase (TPO)
  - TSH receptor
- Auto antibodies can :

➢Produce inflammation and destruction of thyroid tissue (eg TPO Ab)→ hypothyroidism

➢May stimulate the TSH receptor to cause thyrotoxicosis (TRAb or TSI)→ Grave's disease



Classification of Thyroiditis:

Autoimmune thyroiditis

a. Chronic autoimmune thyroiditis:
   - Hashimoto's thyroiditis
   - Atrophic thyroiditis
   - Focal thyroiditis
     - Juvenile thyroiditis

b. Silent thyroiditis

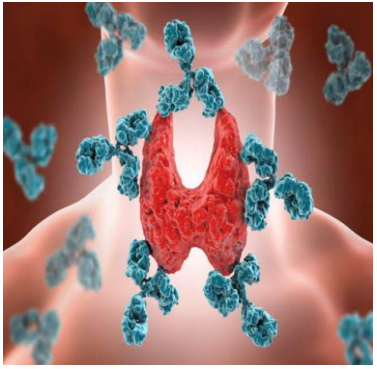
c. Postpartum thyroiditis

4. Riedel's thyroiditis

HASHIMOTO'S THYROIDITIS

Hashimoto's disease is an inflammation of the thyroid gland. It is a condition of inflammation and hormone reduction that occurs as a result of the body attacking the thyroid gland.

The disease causes the thyroid gland to work less and thyroid hormones decrease.



ETIOLOGY

- Hakaru Hashimoto/1912
- Not known exactly
- Thyroid autoantibodies
  - Thyroid Stimulant Antibodies(TRab)
  - Anti-thyroglobulin
  - Anti-peroxidase

What is the mechanism of Hashimoto thyroiditis formation?

The defense system, which must defend the body against alien cells, sometimes attacks the body cells itself, which must protect them by unknown mechanisms. Initially mild, then intensified over time as a result of this attack inflammation of the thyroid gland occurs.The inflamed thyroid gland accumulates a large amount of immune system cells. The accumulated cells are "lymphocytes".

In Hashimoto's thyroiditis, cellular immunity is impaired as a result of genetic defects in suppressor T cells. As a result of this defect, suppressor T lymphocytes cannot suppress auxiliary T lymphocytes. Activated helper T lymphocytes interact with B lymphocytes and secrete many cytokines, including interferon-gamma (INF-γ).

Pathogenesis of Hashimoto's Thyroiditis (HT)

Normal Thyroid

Activated helper (CD4+) T cells

Help B cells produce thyroid specific autoantibodies

Induce formation of CD8+ T cells

Antibodies identified in HT:

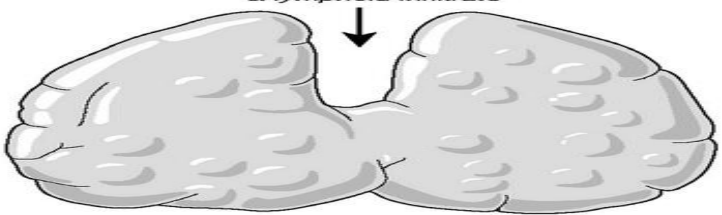
- *antimicrosomal antibody*
- *antithyroglobulin antibody*
- *antibody to TSH receptor*
- *antibody to iodine transporter*

Antibody-dependent cytotoxicity

Thyroid cytotoxicity

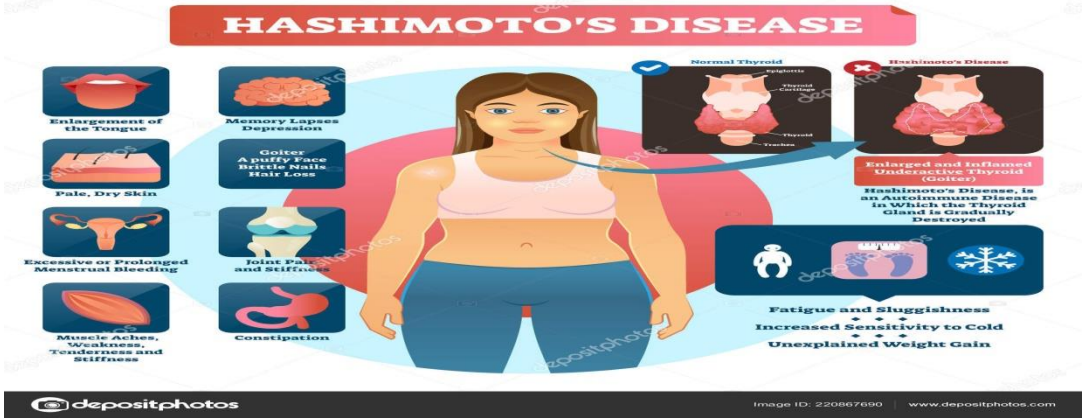
Fas-FasL mediated apoptosis of thyroid follicular cell

Destruction of thyroid parenchyma/fibrosis & lymphoid infiltrate



Hashimoto's Thyroiditis

Autoimmune thyroiditis includes a wide spectrum from Hashimoto's disease (with goiter) to atrophic lymphocytic thyroiditis (without goiter). These diseases change according to the production of antithyroid antibodies of different types



HASHIMOTO'S THYROIDITIS

Hypothyroidism

Autoimmune

Synthroid treatment

Hürthle cell change

Initial Hashitoxicosis

Marginal zone NHL

g**O**iter

TPO (Anti-microsomal) & anti-thyroglobulin antibodies

lymph**O**cytic infiltrate

Epidemiology

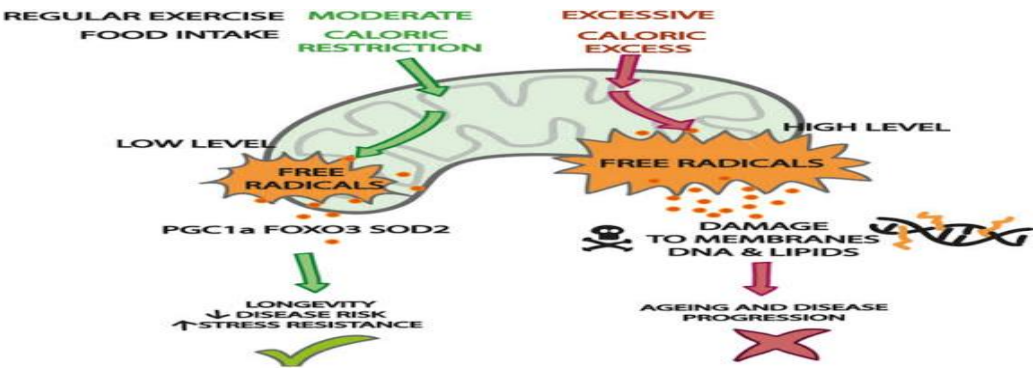
- It is the most common cause of hypothyroidism in America after 6 years of age.
- It is the most common cause of hypothyroidism in regions without iodine deficiency.
- Incidence in America
- 1.3% in children aged 11-18
- Adults :

  Women ‰ 3,5

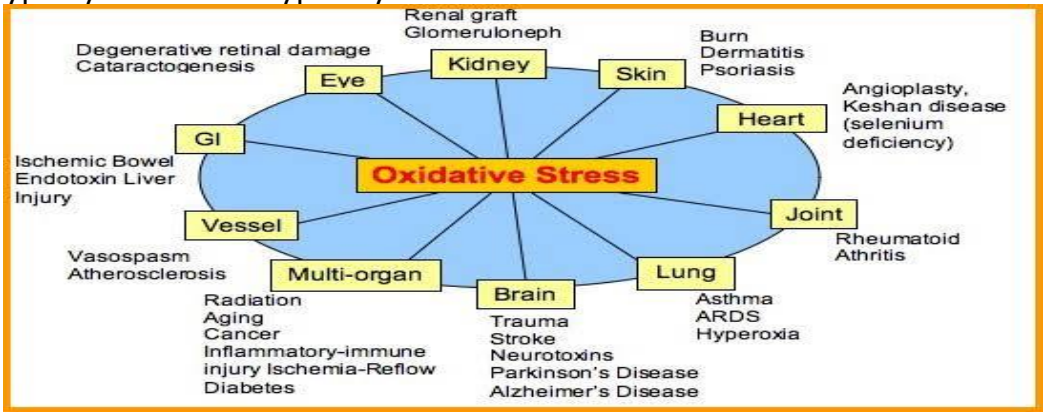
  In men ‰ 0,8
- Worldwide incidence ‰ 0.3-1.5
- 10-15 times more common in women
- Peaks 30-40 years old
- Men peak after 10-15 years
- Incidence increases with age.

OXIDATIVE STRESS

Oxidative stress is an imbalance between free radicals and antioxidants in your body. Free radicals are oxygen-containing molecules with an uneven number of electrons. The uneven number allows them to easily react with other molecules.

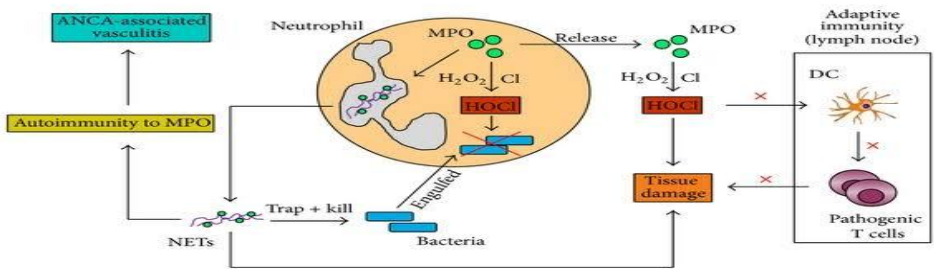


It was reported that free radicals were responsible for the complications observed in the pathogenesis of thyroid diseases and later stages of the disease. As a result of disruptions in thyroid hormone metabolism, basal metabolic rate changes. Oxidative / antioxidant balance may be impaired in case of hypothyroidism and hyperthyroidism.



MPO (myeloperoxidase)

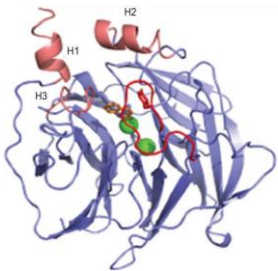
MPO,which is released during inflammation is an oxidative enzyme present in phagocytes.MPO could be a key element responsible for oxidative damage in the artery wall

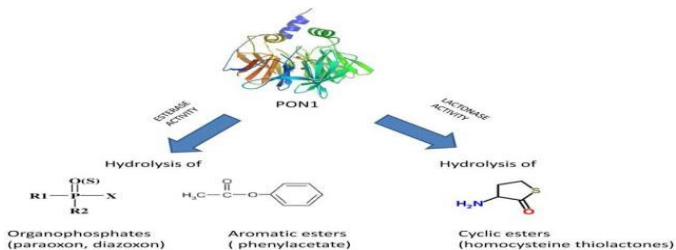


PON1 (Paraoxonase1)

Paraoxonase 1 (PON1) is a hydrolytic enzyme with wide range of substrates, and capability to protect against lipid oxidation. Despite the large number of compounds that can be hydrolyzed by paraoxonase, the biologically relevant substrates are still not clearly determined.

PON1 attracted significant interest as a protein that is responsible for the most of antioxidant properties of high-density lipoprotein (HDL).





HDL-associated

HDL refers to high-density lipoproteins. This is called "good" cholesterol because; It is because of its ability to take excess cholesterol in tissues and metabolize it from the body and transport it to the liver for disposal.

PON-1,which is one of the molecules that play a role in oxidant balance, is an enzyme that has the role of inhibiting lipoprotein oxidation by hydrolzing lipid peroxides in oxidized LDL structure. We investigated the role of HDL-associated MPO and PON-1 patients with HT in terms of coronary artery disease.

OBJECTIVES

The aim of this study is to establish the relationship of HDL with MPO and PON-1 in the Hashimoto's thyroid and to determine its relationship with coronary artery disease.

Materials and Methods

The study was conducted in Hitit University Faculty of Medicine Department of Internal Medicine and two centers with Molecular biology and genetics department.Anamnesis and consent forms were obtained from the patients.Work permit was obtained from Hitit University Clinical Research Ethics Committee.Our study group consisted of 54 patients with Hashimoto diagnosis and 28 healthy individuals as control groups. MPO and PON-1 levels were determined spectrophotometrically.

Inclusion criteria of volunteer patients;

•Accepting the study and signing the informed consent form,
• Being between 18-65 years,
• Not to be pregnant,
• Diagnosing Hashimoto thyroiditis,
•Not having any other disease,
•At least one of anti-thyroid peroxidase antibody (anti-TPO) and anti-thyroglobulin antibody (anti-Tg) is positive,

Voluntary Control group inclusion criteria; Accepting the study and signing the informed consent form,

• Being between 18-65 years,
•Not to be pregnant,
• Not to be diagnosed with Hashimoto's thyroiditis,
• Not having any disease,
• Anti-thyroid peroxidase antibody (anti-TPO) and anti-thyroglobulin antibody (anti-Tg) are both negative,

Exclusion Criterion;

•Classification of volunteers for research
•Under 18 and older than 65
• Pregnant,
•BMI> 30 should not be a risk factor for atherosclerosis such as diabetes mellitus, hypertension, chronic renal failure, chronic disease insufficiency, severe hyperlipidemia (LDL> 190, familial hyperlipidemia), coronary artery disease.
• Safety of any cancer and other autoimmune diseases, primary hyperparathyroidism
• Those who have undergone thyroid surgery

RESULTS

Table 1.

		Age#	TSH	ST3#	ST4	AntiTPO	AntiTroglobulin	CRP
Patients	Mean±S.D	37.8±11.4	8.2±12.8	2.9±.47	1.2±.29	1031±503	196.6±164.8	5.53±5.25
	SEM	11.4	2.6	.09	.05	100	32.9	1.1
Control	Mean±S.D	41.2±12.0	2.2±1.2	3.35±0.46	1.15±0.14	30.5±5.22	28.8±11.1	4.48±3.8
	SEM	2.5	0.24	0.1	0.03	1.1	2.26	0.76
	U	-	187.000	-	273.000	.000	12.000	166.000
	p*	.326	.024	.002	.589	.000	.000	.005

OneWay-Anova were used for Age, ST3, Total Cholestherol and LDL data according to Shapiro wilk test results; p>.005)

Mann Whitney U test was used for other parameters.

Table 2.

		Total Cholestherol#	LDL#	HDL	Trigliseride
Control	Mean±S.D	188.8±42.9	113.3±33.7	57.7±14.1	103.6±46.5
	SEM	8.6	6.7	2.8	9.3
Patients	Mean±S.D	193.4±36.3	116.7±29.9	53.2±15.0	112.0±49.9
	SEM	7.4	6.11	3.1	10.1
	U	-	-	300.000	280.000
	p*	.684	.712	.784	.698

OneWay-Anova were used for Age, ST3, Total Cholestherol and LDL data according to Shapiro wilk test results; p>.005)

Mann Whitney U test was used for other parameters.

Table 3.

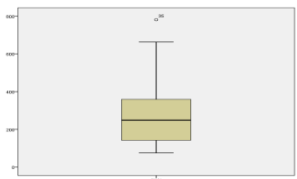
		PON	MPO
Control	Mean±S.D	276.0±187.6	82.0±41.2
	SEM	37.5	8.4
Patients	Mean±S.D	156.6±71.5	110.5±39.7
	SEM	14.7	8.1
	U	176.000	181.500
	p*	.013	.018

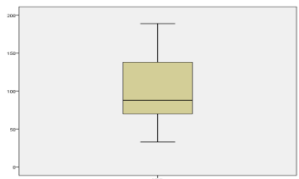
RESULTS

When the study groups were evaluated, PON-1 levels were significantly lower in patients with Hashimoto Thyroiditis than healthy subjects($p<0.05$, $p=0.013$).

When the study groups were evaluated,MPO levels were significantly higher in patients with Hashimoto Thyroiditis than the control group ($p<0.05$, $p=0.018$).

A negative correlation was obtained between MPO and PON-1 ($r=-0.148$).





CONCLUSIONS

The decrease in PON-1 activity and increase in MPO activity due to hypothyroid effect increases lipid peroxide formation and accelerates oxi LDL formation,which leads to decrease in antioxidant capacity and development of atherosclerosis.

Since oxidative stress in thyroid diseases is also responsible for the complications observed in the later stages of the disease,we think that important data were obtained with this study in terms of both diagnosis and treatment.

Thanks for listening to my presentation