

---

Jasmina Aleksić<sup>1</sup>

## **THE INFLUENCE OF VITAMIN D AND IRON ON THYROID FUNCTION AND THYROID AUTOIMMUNITY**

Consideration of autoimmunity as a cause of disease began when immunology itself began in 1901 with Ehrlich's term Horror autotoxicus. Three years later, the cold autoantibody autohemolysin was described, responsible for paroxysmal hemoglobinuria, but without forming any lasting concept of autoimmunity as the cause of this disease. Ehrlich's doctrine admittedly did not help in accepting the concept of autoimmunity, nor did the focus of immunology in that period on external causes instead of internal ones. Between 1915 and 1945, immunology turned to other fields of research, although studies related to autoimmunity were carried out, and in 1945 there was an expansion of autoimmunity research. The term was generally accepted only around 1965 (1).

*Autoimmune diseases* represent a spectrum of diseases caused by inflammation, due to the production of autoantibodies and the consequent cytotoxic action of T lymphocytes. Data indicate differences in the prevalence of autoimmune diseases between Europe, North America, Australia and New Zealand (defined as zone 1) and Asia, the Middle East, the Caribbean and South America (zone 2) (2). In most autoimmune diseases, women make up >85% of patients. Only in some autoimmune diseases with childhood presentation, such as diabetes mellitus type 1, the risk of the disease is equal for both sexes. There are three peaks for the onset of autoimmune diseases: between the ages of 8 and 10 (juvenile rheumatoid arthritis, DM type 1), between the ages of 33 and 50 (myasthenia gravis, multiple sclerosis, SLE, scleroderma, Graves' disease) and between the ages of 52 and 63 (Hashimoto's thyroiditis, adult rheumatoid arthritis) (3).

*Autoimmune diseases of the thyroid gland* are the most prevalent organ-specific diseases and affect 2-5% of the population (4), with great variability between the sexes (5-15% of women, 1-5% of men) (5). The two most significant entities within autoimmune thyroid diseases are Hashimoto's thyroiditis and Graves' disease. These diseases are the result of loss of immune tolerance of own antigens. There is a cellular

---

<sup>1</sup> Medigroup Bulevar, Health Centre

and humoral immune response against thyroid gland antigens with reactive infiltration of T and B lymphocytes, production of autoantibodies and then the development of clinical manifestations of the disease (6, 7). These are diseases of multifactorial etiology, with a complex interaction between environmental factors and genetic predisposition (8).

Genetics play a significant role in the pathogenesis of autoimmune thyroid diseases. Some of the genes responsible for these autoimmune diseases are common to Hashimoto's and Graves' disease, while genes specific to one of these 2 diseases have also been identified (9). The association between HLA genes and these diseases is well known. This explains some similarities in the pathological findings between Hashimoto's thyroiditis and Graves' disease, because in both diseases the presentation is dependent on certain HLA-B and HLA-DR, which suggests that hereditary risk factors are important in the pathogenesis of these diseases (10, 11). In addition to HLA genes, other genes responsible for the immune system are also responsible for the development of all autoimmune diseases, as well as autoimmune diseases of the thyroid gland, which speaks in favor of genetic susceptibility to autoimmune diseases. Polymorphisms in certain CTLA-4 alleles are associated with a predisposition to Hashimoto's thyroiditis and Graves' disease (12–16). In a study conducted on 379 patients in Great Britain, 42% of patients in the test group had the G allele of the CLA-4 gene, while 32% in the control group had that allele (16). This genetic abnormality was associated with stimulation of thyroid antibody production and clinical presentation of autoimmune thyroiditis in interaction with other loci also responsible for genetic predisposition to this disease (6, 13, 16, 17). CD40 is found only on follicular cells of the thyroid gland and on B lymphocytes. The polymorphism of this gene is associated with a 20-30% increase in translation of the mRNA transcript of CD40 in patients with autoimmune thyroid diseases (18). Polymorphism of the PTPN22 gene, which encodes a negative regulator of T lymphocyte activation, has been linked to both autoimmune diseases of the thyroid gland and autoimmune diseases in general (9). Abnormalities in the FOXP3 gene, which is responsible for the differentiation of T lymphocytes into Treg cells, have been linked to the juvenile form of Graves' disease (19). Changes in the CD25 gene are also associated with Graves' disease (20).

Although the link between genetic susceptibility and environmental factors thyroiditis is clear, the mechanism by which genetic variability interacts with environmental factors in autoimmune diseases is still not fully understood. Recent data point to the role of epigenetic mechanisms. Epigenetic modulation of gene expression can be manifested by changes in DNA methylation, histone modification (acetylation, deacetylation, methylation), as well as RNA interference via microRNA molecules. More recently, it has been shown that IFN- $\alpha$  induces alteration in the thyroglobulin gene through epigenetic changes in histones (21). Given that IFN- $\alpha$  is secreted locally during viral infections, this could explain the mechanism by which infections could trigger the

development of autoimmune thyroid diseases (22). Another epigenetic phenomenon described in the pathogenesis of autoimmune diseases of the thyroid gland is the inactivation of the X chromosome. The degree of inactivation of the X chromosome is a significant factor in the increased tendency of women to these autoimmune diseases, according to the study by Yin et al. (23).

Numerous environmental factors are associated with the occurrence of autoimmune thyroid diseases such as low birth weight, iodine excess, selenium deficiency, stress, smoking, allergies, radiation exposure, drugs, viral or bacterial infections, as well as fetal microchimerism (24). Smoking is one of the more important environmental factors related to this disease, if not the most important factor (25). Cigarette smoke contains cyanide, which is metabolized to thiocyanate, which can disrupt iodine concentrations in the thyroid gland (26). There is evidence to suggest that the involvement of infections in the pathogenesis of these diseases is very significant. However, even non-pathogenic microorganisms, normal inhabitants of the human microflora, induce a pro-inflammatory or regulatory immune response in the host (27). There are data that *B. Burgdoferi* and *Y. Enterocolitica* are frequent triggers of thyroid autoimmunity. Molecular mimicry is hypothesized to be the way in which these two microorganisms elicit an autoimmune response (28, 29). Some other microorganisms that are assumed to play the role of triggers in autoimmune diseases of the thyroid gland are *H. Pylori*, Coxsackie virus, hepatitis C virus and retroviruses (29).

Although iodine is necessary for the functioning of the thyroid gland, it is also one of the most important causes of thyroid dysfunction. A mild iodine deficiency is associated with a reduced prevalence of Hashimoto's thyroiditis, while a mild excess of this element is associated with a higher prevalence of this autoimmune disease. Potential mechanisms by which iodine could induce thyroid autoimmunity include direct stimulation of the immune response in the thyroid gland, increased immunogenicity of highly iodinated thyroglobulin, and the direct toxic effect of iodine on thyrocytes through the generation of free radicals (30–32). Kahaly et al. followed a group of patients with endemic goiter who received iodine for 6 months and a group with the same condition who received T4. A high titer of thyroid antibodies was found in 16% of patients receiving iodine treatment. After they stopped taking iodine, antibody levels decreased significantly and after 4 years were normal in 4 of 6 patients (30).

The most common manifestation of radiation on the thyroid gland is hypofunction both due to direct destruction of the gland and due to stimulation of thyroid antibodies (29). Autoimmune diseases of the thyroid gland have also occurred with the therapeutic application of radiation (33), as well as with exposure to radiation in the environment (34). In a study conducted on 160 people who were exposed to radiation at the workplace, 10% of them met the criteria for the diagnosis of autoimmune

thyroiditis, while in the control group only 3.4% met the criteria. Subjects who were exposed to radiation for more than 5 years were at greater risk (35).

Many pollutants present in the environment have been shown to cause autoimmune thyroid diseases (36). For example, a high prevalence of hypothyroidism was observed, with elevated values of anti-TPO and anti-Tg, in individuals exposed to polybrominated biphenyls. Bisphenol A, often used in the production of plastics, could bind to the TSHR as a competitive antagonist of T3 (31, 36, 37).

Several drugs play a role in the pathogenesis of autoimmune thyroid diseases. IFN- $\alpha$ , IL-2, lithium, amiodarone, and highly active retroviral therapy are the agents most commonly associated with thyroid dysfunction (29, 31). For most of these drugs, it is true that patients with the highest risk of developing autoimmune thyroiditis are those who, before the use of this therapy, already had elevated levels of thyroid antibodies (29, 31, 36). Some drugs, such as lithium, although not direct triggers of autoimmunity, accelerate autoimmune processes by interfering with the synthesis of thyroid hormones. Thyroid function testing, as well as the measurement of the anti-TPO titer should be considered before the introduction of these drugs into therapy (24).

Mechanisms by which stress could induce thyroid autoimmunity are the induction of immunosuppression by antigen non-specific mechanisms, probably due to the effects of cortisol and CRH on immune cells, which is followed by immune hyperreactivity and consequent autoimmune disease of the thyroid gland. It is believed that postpartum thyroidism has a similar mechanism of origin. However, so far there is no evidence linking stress with thyroid autoimmunity, probably because the stressful event and the damage to this gland itself are separated in time (29, 31, 36).

Fetal cells have been identified in the thyroid glands of mothers suffering from autoimmune thyroiditis. Such cells could cause graft versus host disease in the thyroid gland and thus could play a significant role in the pathogenesis of Hashimoto's thyroiditis (38,39). This mechanism of thyroid autoimmunity is still at the level of a hypothesis.

These diseases are generally accompanied by the presence of anti-TPO (thyroid peroxidase), anti-Tg (thyroglobulin), or anti-TSH receptor antibodies. There are also antibodies against other target antigens (carbonic anhydrase 2, megalin, T3, T4, Na-I transporter, pendrin), but they are rarely encountered in practice (40). Thyroid peroxidase is a weakly glycosylated membrane-bound enzyme responsible for iodine oxidation and iodination of the tyrosyl residue of the thyroglobulin molecule (41). Anti-TPO antibodies from healthy individuals did not block TPO activity (42), while anti-TPO antibodies from patients with autoimmune thyroid diseases destroyed thyrocytes and inhibited the enzymatic activity of TPO by competitive inhibition (43). Anti-TPO antibodies are more common than anti-Tg antibodies and therefore a better indicator of thyroid autoimmunity (44). Anti-TPO antibodies are also an inducer of oxidative stress because they reduce the antioxidant potential (45). Although these antibodies

have a cytotoxic effect on thyrocytes in Hashimoto's thyroiditis, they have no established role in Graves' disease (46).

Thyroglobulin is a large (600kDa) glycoprotein consisting of dimers and an average of 2-3 molecules of T4 and 0.3 molecules of T3. This molecule is heterogeneous in terms of content, glycosylation and structure. Antibody production against Tg can be induced by massive destruction of the thyroid gland, although high levels of Tg in the blood do not necessarily induce antibody production. Of the 40 epitopes on the Tg molecule that have been identified, according to some authors 6 and according to others 1-2 are immunogenic (47, 48). Healthy individuals have low levels of anti-Tg antibodies, generally below the threshold required for laboratory detection. In the presence of elevated serum levels of Tg due to the destruction of thyroid tissue, changed conformation of the thyroglobulin molecule due to high levels of I2 and increased TSH, the titer of anti-Tg antibodies also increases abnormally (48). Administration of I2 to subjects induced anti-Tg antibody production in 8-20% of subjects, associated with intrathyroidal lymphocytic infiltrate in some patients (49).

Hashimoto's thyroiditis is a chronic inflammation of the thyroid gland first described more than 100 years ago, but the etiopathogenesis is still not fully defined (50). It is considered the most common autoimmune disease (51, 52), the most common endocrine disorder (53), as well as the most common cause of hypothyroidism (54, 55).

Hashimoto's thyroiditis was first described by Dr. Hakara Hashimoto in 1912, studying thyroid specimens from 4 middle-aged women who had their glands removed for compressive symptoms. This disease was considered rare until the fifties of the last century, and now it is the most frequent autoimmune disease, with an incidence of 1 per 1,000 people per year, and a prevalence of 8 per 1,000 if the revisions of scientific articles in the field of endocrinology are taken as a source (50), and 46 per 1000 if only biochemically confirmed thyroiditis and thyroid antibodies are considered (56). This autoimmune disease is up to 8 times more common in women than in men, also the white and yellow races suffer more often than the black (50). In 2 Chinese studies, increased dietary iodine intake was correlated with an increased occurrence of Hashimoto's thyroiditis in the population (57, 58). In Denmark, after the introduction of a mandatory salt iodization program, they saw an increase in the prevalence of elevated anti-TPO antibodies as well as Hashimoto's thyroiditis (59). Etiologically, this disease can be divided into primary and secondary forms.

Primary thyroiditis includes all cases without a clear etiology. Clinically-pathologically, primary Hashimoto's thyroiditis includes 6 entities: classic form (60), fibrotic form, IgG4 variant (61), juvenile form (62), Hashitoxicosis and painless (silent) thyroiditis (occurs as isolated and postpartum) (63). Clinically, the most common manifestation is enlargement of the thyroid gland (goiter), which goes with or without accompanying hypothyroidism. The most common pathological finding is significant lymphocytic infiltration of the thyroid gland. Primary Hashimoto's thyroiditis can manifest itself as an isolated disease, but it can often occur together with

various other autoimmune diseases (diabetes type 1, Sjogren's syndrome), or thyroid gland diseases. Among the diseases of the thyroid gland, it is important to mention the association between primary Hashimoto's thyroiditis and papillary carcinoma of the thyroid gland, which is between 0.5 and 30%, depending on the source (60,64).

Secondary thyroiditis are forms of this disease with an established etiological agent. Most often, they are of iatrogenic origin, as a consequence of immunomodulatory drug therapy (eg the use of interferon- $\alpha$  in hepatitis C therapy) (65). During the past 10 years, the development of anticancer immunotherapy has led to the emergence of many immune-mediated diseases, including thyroiditis, which can be seen in the use of monoclonal antibodies that block CTLA-4 (66), as well as in the example of vaccines against malignant diseases (67).

Hashimoto's thyroiditis is a prototype organ-specific autoimmune disease. Often, patients with this disease either have other autoimmune diseases, or have someone in the family with other diseases of this type (68), which indicates the genetic origin of these diseases. Hashimoto's thyroiditis (69) and systemic lupus (70) are the first two autoimmune diseases for which a genetic component was proven in the early seventies of the last century, in the genes for MHC class II proteins. However, in the last 4 decades, only a few more genes associated with the tendency to thyroiditis have been found, although the mechanism by which they influence the occurrence of this disease has not been established (71).

In Hashimoto's thyroiditis, both thyrocytes and the interstitium surrounding the follicles are affected. The classic form of this disease is mainly presented by an enlarged, grayish thyroid gland, with characteristic interstitial infiltration by predominantly lymphocytes with some plasma cells and macrophages (50). Within the gland, lymphocytes are organized into lymph follicles (tertiary, ectopic), with all the structural characteristics of a true lymph follicle. Fibrosis of the interstitium also occurs. Thyrocytes are atrophic in some parts of the gland, and enlarged in others, with a hyperchromatized nucleus and a cytoplasm full of mitochondria (72). Fibrous type of thyroiditis is characterized by an enlarged, hard and lobulated thyroid gland. Fibrosis in this disease does not break through the capsule, in contrast to Riedel's thyroiditis, in which adhesions of the gland to the surrounding structures occur. Chronic inflammation of lymphocytes, also organized into follicles, occurs in this type as well. In the late stage of the disease, as in older patients, the fibrous variant manifests as idiopathic myxedema, where the thyroid tissue is reduced to a small fibrous bud (50).

The IgG4 variant was first described in Japan in 2009. Pathologically, it is defined by pronounced lympho-plasmacytic infiltration, with the fact that in this variant of the disease, the infiltrate contains a large number of IgG4-producing plasma cells (>20 cells per visual field). Interstitial fibrosis is not expressed as in the previously described two forms.



The other 3 forms (juvenile, Hashitoxicosis, painless thyroiditis) rarely require thyroidectomy, therefore there are not many pathohistological samples taken from patients with these types of diseases. They have characteristics similar to the other forms, with the fact that the fibrosis is milder and the appearance of lymph follicles is not so common.

The diagnosis of Hashimoto's thyroiditis is made on the basis of clinical features, the presence of serum antibodies against thyroid antigens (anti-TPO, anti-TG) as well as findings of ultrasound of the thyroid gland. Additional tests that are performed less often, but contribute to better diagnosis, are scintigraphy of the thyroid gland to detect uptake of radioactive iodine isotope in the thyroid gland, as well as cytological examination of thyroid aspirate (50).

The manifestations of Hashimoto's thyroiditis vary according to the nature of the disease itself. Initially, patients may have hyperthyroid symptoms, caused by the initial destruction of thyroid cells and the subsequent release of thyroid hormones into the bloodstream. When the released hormones are metabolized, due to the destruction of thyroid cells, hypothyroidism occurs. The symptoms of hypothyroidism are insidious, variable and can affect almost any organ or organ system in the body.

Skin manifestations include dry skin, especially on the extensor sides of the hands and feet, pale skin due to accumulation of dermal mucopolysaccharides and consequent greater water retention, as well as myxedema in more severe forms of this disease. Hair growth is slowed, and hair is often brittle and dry. Alopecia is also a relatively common manifestation. Peripheral vascular resistance can drop up to 60%, and cardiac output can decrease up to 50%. Bradycardia may also occur. Fatigue, dyspnea on exertion, as well as exertion intolerance occur due to limited pulmonary and cardiac reserve, as well as due to muscle weakness. Early symptoms may include constipation, fatigue, dry skin, and weight gain. In the later stages of the disease, there is cold intolerance, reduced sweating, peripheral neuropathies, lack of energy, depression, dementia, memory loss, muscle spasms, joint pain, hair loss, apnea, menorrhagia, as well as compressive symptoms in the neck area due to an enlarged thyroid gland and hoarseness. During the examination, attention should be paid to cold and dry skin, periorbital edema, brittle nails, bradycardia, delayed tendon reflex relaxation phase, increased blood pressure, slowed speech, ataxia and macroglossia (73).

*Vitamin D* is a steroid molecule produced mainly in the skin, which regulates the expression of a large number of genes (74). There are two forms of vitamin D, vitamin D3 (cholecalciferol), and vitamin D2 (ergocalciferol). Cholecalciferol is produced in the skin after exposure to UVB radiation, although it can also be found in some foods such as some fatty fish, while ergocalciferol is produced by plants and fungi (75, 76). Vitamin D is incorporated from the digestive tract into chylomicrons, which reach the lymphatic system and then the venous blood. This vitamin, whether from the skin or from the diet, is biologically inert until it undergoes its first

hydroxylation in the liver to form 25(OH)D. Vitamin D requires another hydroxylation in the kidneys, when the biologically active form of vitamin D 1,25(OH)<sub>2</sub>D is formed (77). This active form of vitamin D stimulates the intestinal absorption of calcium. Without vitamin D, only 10–15% of calcium and about 60% of phosphorus are absorbed from food (77, 78). The receptor for vitamin D is found in almost all tissues and cells in the body. 1,25(OH)<sub>2</sub>D has a wide range of effects in the body, such as inhibition of cell proliferation, induction of terminal cell differentiation, inhibition of angiogenesis, stimulation of insulin production and inhibition of renin production (79–81). The biologically active form of vitamin D is responsible for the activation and suppression of between 200 and 500 genes, which constitutes about 3% of the human genome (82). The main role of vitamin D is regulation of bone metabolism and regulation of calcium and phosphorus homeostasis. Recent research has shown that vitamin D deficiency, which is widespread, could also have manifestations beyond the bone system, in the form of autoimmune diseases, tumors, metabolic syndromes, etc. (74, 83, 84). Low serum vitamin D levels are also associated with autoimmune thyroid diseases such as Hashimoto's thyroiditis and Graves' disease (82, 85, 86). Autoimmune diseases of the thyroid gland are caused by a combination of genetic predisposition and triggers from the environment (Iodine, Selenium, drugs, smoking, infections, stress). These diseases are characterized by lymphocytic infiltration of the thyroid gland and the production of specific antithyroid antibodies (87, 88). In genetically predisposed individuals, the disruption of immune-endocrine interactions by environmental factors leads to an imbalance between Th1 and Th2 immune responses. This results in a Th1 cell-mediated autoimmune reaction with thyrocyte destruction and hypothyroidism in Hashimoto's thyroiditis, and a hyperreactive Th2-mediated humoral response directed at the TSH receptor with stimulatory antibodies leads to hyperthyroidism in Graves' disease (87). Vitamin D plays a significant role in modulating the immune response, enhancing the native and inhibiting the acquired immune response (75, 89). Most immune cells, primarily T lymphocytes, B lymphocytes, APCs such as dendritic cells and macrophages have VDR (vitamin D receptor) and 1 $\alpha$ -hydroxylase (75,76,90). At the level of antigen-presenting cells, 1,25(OH)<sub>2</sub>D inhibits the surface expression of MHC class II proteins and costimulatory molecules and prevents the differentiation and maturation of dendritic cells as well as their activation and survival, which leads to a decrease in antigen presentation and cellular activity. Also, 1,25(OH)<sub>2</sub>D indirectly inhibits the production of IL-12 and IL-23, and promotes the release of IL-10. Therefore, 1,25(OH)<sub>2</sub>D indirectly shifts the balance of the immune response from Th1 and Th17 immune responses, to Th2 immune responses (90, 91). 1,25(OH)<sub>2</sub>D inhibits the proliferation, differentiation and production of cytokines (IL-2 and interferon- $\gamma$ ) of Th1 cells, as well as Th-17 cytokines (IL-17 and IL-21), but also promotes the production of anti-inflammatory Th2 cytokines (IL-3, IL-4, IL-5 and IL-10). The active form of vitamin D also inhibits the proliferation of B lymphocytes and their differentiation into plasma cells, suppresses the secretion of



immunoglobulins (IgG and IgM), prevents the formation of memory B lymphocytes and induces apoptosis of B lymphocytes (75, 76, 89–92). The ability of  $1,25(\text{OH})_2\text{D}$  to suppress the acquired immune system helps develop immune tolerance and has been shown to be beneficial in a number of autoimmune diseases (75, 76).

*Iron* is an important micronutrient for maintaining cellular energy and metabolism (93). Iron is widely distributed on Earth and is an essential component of every living organism (94, 95). Despite the widespread distribution of this element, iron is often a limiting factor in the environment (96). This apparent paradox is a consequence of iron's ability to form oxides in contact with oxygen, which are very insoluble and therefore unavailable for absorption by the living world. Various cellular mechanisms have been developed so that iron from the environment can be used in a biologically useful form. Siderophores secreted by microorganisms (97), as well as the mechanisms for the reduction of iron from the insoluble trivalent to the soluble divalent form in some yeasts (98) are good examples of the aforementioned cellular mechanisms.

Iron occurs in the diet in 2 forms: Heme and non-Heme. The primary source of heme iron is hemoglobin and myoglobin from meat and fish, while non-heme iron is present in grains, legumes, fruits and vegetables. Heme iron has a better availability from food (15–35%) than non-heme iron (2–20%) (99). Admittedly, non-heme iron is present to a greater extent in the diet, so regardless of its poor utilization, more iron in this form is taken into the body than in the Heme form (100).

Iron deficiency manifests as low serum iron and lower ferritin levels. It is considered the most common nutritional deficiency and can lead to undesirable effects on thyroid metabolism in women of reproductive age as well as pregnant women (101, 102). Research has shown that iron deficiency negatively affects thyroid function by interfering with oxygen transport or affecting thyroid peroxidase activity (103, 104). According to some studies, iron deficiency doubles the risk of developing hypothyroidism (105, 106). It should be emphasized that these studies did not examine the association between iron deficiency and thyroid autoimmunity.

Regarding the effect of iron deficiency on the levels of antibodies to thyroid antigens (anti-TPO, anti-Tg, anti-TSH), one study says that the presence of these antibodies is more often seen in subjects with a deficiency of this micronutrient (107), while others say that even in subjects with a deficiency, antithyroid antibodies are less often seen (108). Studies showing an association between thyroid autoimmunity and iron deficiency are rare (109, 110). Studies in rats have shown that iron deficiency reduces serum thyroid hormone concentrations by reducing hepatic thyroxine deiodinase activity, disrupting peripheral conversion of T4 to T3, and reducing the TSH response to TRH.

Iron deficiency is thought to affect thyroid hormone feedback, stimulating the pituitary gland to secrete TSH. Also, iron plays an important role in the normal functioning of thyroperoxidase (TPO), a heme-dependent protein. Iron also participates in enhancing the action of iodine in the thyroid gland (112, 113).

## References

1. Mackay IR. Travels and travails of autoimmunity: A historical journey from discovery to rediscovery. *Autoimmunity Reviews*. 2010 Mar; 9(5).
2. Cooper GS, Bynum MLK, Somers EC. Recent insights in the epidemiology of autoimmune diseases: improved prevalence estimates and understanding of clustering of diseases. 2009; 33(3–4): 197–207.
3. Cooper GS, Stroehla BC. The epidemiology of autoimmune diseases. *Autoimmun Rev*. 2003; 2(3): 119–25.
4. Simmonds MJ, Gough SCL. Unravelling the genetic complexity of autoimmune thyroid disease: HLA, CTLA-4 and beyond. *Clin Exp Immunol*. 2004; 136(1): 1–10.
5. Dayan CM, Daniels GH. Chronic autoimmune thyroiditis. *N Engl J Med*. 1996; 335(2): 99–107.
6. Tomer Y, Davies TF. Searching for the autoimmune thyroid disease susceptibility genes: from gene mapping to gene function. *Endocr Rev*. 2003; 24(5): 694–717.
7. Anaya JM, Castiblanco J, Rojas-Villarraga A, Pineda-Tamayo R, Levy RA, Gómez-Puerta J, et al. The multiple autoimmune syndromes. A clue for the autoimmune tautology. *Clin Rev Allergy Immunol*. 2012; 43(3): 256–64.
8. Anaya JM, Rojas-Villarraga A, García-Carrasco M. The autoimmune tautology: from polyautoimmunity and familial autoimmunity to the autoimmune genes. *Autoimmune Dis*; 2012.
9. Thyroid disease and autoimmune diseases - Autoimmunity - NCBI Bookshelf.
10. Ban Y, Davies TF, Greenberg DA, Concepcion ES, Tomer Y. The influence of human leucocyte antigen (HLA) genes on autoimmune thyroid disease (AITD): results of studies in HLA-DR3 positive AITD families. *Clin Endocrinol (Oxf)*. 2002.
11. Kologlu M., Fung H., Darke C., Richards CJ, Hall R., McGregor AM. Postpartum thyroid dysfunction and HLA status. *Eur J Clin Invest*. 1990; 20(1): 56–60.
12. Kotsa K, Watson PF, Weetman AP. A CTLA-4 gene polymorphism is associated with both Graves disease and autoimmune hypothyroidism. *Clin Endocrinol (Oxf)*. 1997; 46(5): 551–4.
13. Villanueva R, Greenberg DA, Davies TF, Tomer Y. Sibling recurrence risk in autoimmune thyroid disease. *Thyroid*. 2003; 13(8): 761–4.
14. Yanagawa T, Hidaka Y, Maraes VG, Soliman M, Degroot LJ. CTLA-4 gene polymorphism associated with Graves' disease in a Caucasian population. *J Clin Endocrinol Metab*. 1995; 80(1): 41–5.
15. Kacem HH, Rebai A, Ayadi H, Farid NR. The genetics of autoimmune thyroid disease. *J Clin Endocrinol Metab*. 2002; 87(12): 115–28.
16. Heward JM, Allahabadia A, Armitage M, Hattersley A, Dodson PM, Macleod K, et al. The development of Graves' disease and the CTLA-4 gene on chromosome 2q33. *J Clin Endocrinol Metab*. 1999; 84(7): 2398–401.
17. Vieland VJ, Huang Y, Bartlett C, Davies TF, Tomer Y. A multilocus model of the genetic architecture of autoimmune thyroid disorder, with clinical implications. *Am J Hum Genet*. 2008; 82(6): 1349–56.

18. Jacobson EM, Concepcion E, Oashi T, Tomer Y. A Graves' disease-associated Kozak sequence single-nucleotide polymorphism enhances the efficiency of CD40 gene translation: a case for translational pathophysiology. *Endocrinology*. 2005; 146(6): 2684–91.
19. Tomer Y, Menconi F, Davies TF, Barbesino G, Rocchi R, Pinchera A, et al. Dissecting genetic heterogeneity in autoimmune thyroid diseases by subset analysis. *J Autoimmun*. 2007; 9(2–3): 69–77.
20. Brand OJ, Lowe CE, Heward JM, Franklyn JA, Cooper JD, Todd JA, et al. Association of the interleukin-2 receptor alpha (IL-2Ralpha)/CD25 gene region with Graves' disease using a multilocus test and tag SNPs. *Clin Endocrinol (Oxf)*. 2007; 66(4): 508–12.
21. Stefan M, Jacobson EM, Huber AK, Greenberg DA, Li CW, Skrabanek L, et al. Novel variant of thyroglobulin promoter triggers thyroid autoimmunity through an epigenetic interferon alpha-modulated mechanism. *J Biol Chem*. 2011; 286(36): 31168–79.
22. Hasham A, Tomer Y. Genetic and epigenetic mechanisms in thyroid autoimmunity. *Immunol Res*. 2012; 54(1–3): 204–13.
23. Yin X, Latif R, Tomer Y, Davies TF. Thyroid epigenetics: X chromosome inactivation in patients with autoimmune thyroid disease. *Ann N Y Acad Sci*. 2007; 1110: 193–200.
24. Prummel MF, Strieder T, Wiersinga WM. The environment and autoimmune thyroid diseases. *Eur J Endocrinol*. 2004; 150(5): 605–18.
25. Bahn RS. Graves' ophthalmopathy. *N Engl J Med*. 2010; 362(8): 726–38.
26. Pearce EN, Braverman LE. Environmental pollutants and the thyroid. *Best Pract Res Clin Endocrinol Metab*. 2009; 23(6): 801–13.
27. Mori K, Yoshida K. Viral infection in induction of Hashimoto's thyroiditis: A key player or just a bystander? *Current Opinion in Endocrinology, Diabetes and Obesity*. 2010 Oct; 17(5): 418–24.
28. Benvenga S, Santarpia L, Trimarchi F, Guarneri F. Human thyroid autoantigens and proteins of *Yersinia* and *Borrelia* share amino acid sequence homology that includes binding motifs to HLA-DR molecules and T-cell receptor. *Thyroid*. 2006; 16(3): 225–36.
29. Eschler DC, Hasham A, Tomer Y. Cutting edge: the etiology of autoimmune thyroid diseases. *Clin Rev Allergy Immunol*. 2011; 41(2): 190–7.
30. Kahaly GJ, Dienes HP, Beyer J, Hommel G. Iodide induces thyroid autoimmunity in patients with endemic goitre: a randomised, double-blind, placebo-controlled trial. *Eur J Endocrinol*. 1998; 139(3): 290–7.
31. Burek CL, Talor M v. Environmental triggers of autoimmune thyroiditis. *J Autoimmun*. 2009; 33(3–4): 183–9.
32. Walsh JP, Ward LC, Burke V, Bhagat CI, Shiels L, Henley D, et al. Small changes in thyroxine dosage do not produce measurable changes in hypothyroid symptoms, well-being, or quality of life: results of a double-blind, randomized clinical trial. *J Clin Endocrinol Metab*. 2006; 91(7): 2624–30.
33. Dunkelmann S, Wolf R, Koch A, Kittner C, Groth P, Schuemichen C. Incidence of radiation-induced Graves' disease in patients treated with radioiodine for thyroid autonomy before and after introduction of a high-sensitivity TSH receptor antibody assay. *Eur J Nucl Med Mol Imaging*. 2004; 31(10): 1428–34.

34. Agate L, Mariotti S, Elisei R, Mossa P, Pacini F, Molinaro E, et al. Thyroid autoantibodies and thyroid function in subjects exposed to Chernobyl fallout during childhood: evidence for a transient radiation-induced elevation of serum thyroid antibodies without an increase in thyroid autoimmune disease. *J Clin Endocrinol Metab.* 2008; 93(7): 2729–36.
35. Völzke H, Werner A, Wallaschofski H, Friedrich N, Robinson DM, Kindler S, et al. Occupational exposure to ionizing radiation is associated with autoimmune thyroid disease. *J Clin Endocrinol Metab.* 2005; 90(8): 4587–92.
36. Brent GA. Environmental exposures and autoimmune thyroid disease. *Thyroid.* 2010; 20(7): 755–61.
37. Barragán-Martínez C, Speck-Hernández CA, Montoya-Ortiz G, Mantilla RD, Anaya JM, Rojas-Villarraga A, et al. Organic solvents as risk factor for autoimmune diseases: a systematic review and meta-analysis. *PLoS One.* 2012; 7(12).
38. Ando T, Davies TF. Clinical Review 160: Postpartum autoimmune thyroid disease: the potential role of fetal microchimerism. *J Clin Endocrinol Metab.* 2003; 88(7): 2965–71.
39. Fugazzola L, Cirello V, Beck-Peccoz P. Microchimerism and endocrine disorders. *J Clin Endocrinol Metab.* 2012; 97(5): 1452–61.
40. Fröhlich E, Wahl R. Thyroid Autoimmunity: Role of Anti-thyroid Antibodies in Thyroid and Extra-Thyroidal Diseases. *Frontiers in Immunolog.* 2017; 521.
41. McLachan SM, Rapoport B, Rapoport B. The molecular biology of thyroid peroxidase: cloning, expression and role as autoantigen in autoimmune thyroid disease. *Endocr Rev.* 1992; 13(2): 192–206.
42. Kohno Y, Yamaguchi F, Saito K, Niimi H, Nishikawa T, Hosoya T. Anti-thyroid peroxidase antibodies in sera from healthy subjects and from patients with chronic thyroiditis: differences in the ability to inhibit thyroid peroxidase activities. *Clin Exp Immunol.* 1991; 85(3): 459–63.
43. Kaczur V, Vereb G, Molnar I, Krajczar G, Kiss E, Farid NR, et al. Effect of anti-thyroid peroxidase (TPO) antibodies on TPO activity measured by chemiluminescence assay. *Clinical Chemistry.* 1997; 43(8): 1392–6.
44. Balucan FS, Morshed SA, Davies TF. Thyroid autoantibodies in pregnancy: their role, regulation and clinical relevance. *J Thyroid Res* 2013.
45. Ruggeri RM, Vicchio TM, Cristani M, Certo R, Caccamo D, Alibrandi A, et al. Oxidative Stress and Advanced Glycation End Products in Hashimoto's Thyroiditis. *Thyroid.* 2016; 26(4): 504–11.
46. DeGroot LJ. Graves' Disease and the Manifestations of Thyrotoxicosis. *Endotext.* 2015.
47. Latrofa F, Ricci D, Grasso L, Vitti P, Masserini L, Basolo F, et al. Characterization of thyroglobulin epitopes in patients with autoimmune and non-autoimmune thyroid diseases using recombinant human monoclonal thyroglobulin autoantibodies. *J Clin Endocrinol Metab.* 2008; 93(2): 591–6.
48. Volpé R. Autoimmune diseases of the endocrine system. *CRC Press;* 1990. 364 p.
49. Cyriac T, Chellappa PM, R. SP, Immanuel A. Prevalence of hypothyroidism and its association with anti-thyroid peroxidase antibody among adult sea food consuming population attending a tertiary health care centre in Kerala. *International Journal of Biomedical and Advance Research.* 2015; 6(9): 648–55.

50. Caturegli P, de Remigis A, Rose NR. Hashimoto thyroiditis: Clinical and diagnostic criteria. *Autoimmunity Reviews*. 2014; 13(4–5): 391–7.
51. Jacobson DL, Gange SJ, Rose NR, Graham NMH. Epidemiology and estimated population burden of selected autoimmune diseases in the United States. *Clin Immunol Immunopathol*. 1997; 84(3): 223–43.
52. McLeod DSA, Cooper DS. The incidence and prevalence of thyroid autoimmunity. *Endocrine*. 2012; 42(2): 252–65.
53. Golden SH, Robinson KA, Saldanha I, Anton B, Ladenson PW. Clinical review: Prevalence and incidence of endocrine and metabolic disorders in the United States: a comprehensive review. *J Clin Endocrinol Metab*. 2009; 94(6): 1853–78.
54. Delemer B, Aubert JP, Nys P, Landron F, Bouée S. An observational study of the initial management of hypothyroidism in France: the ORCHIDÉE study. *European Journal of Endocrinology*. 2012; 167(6): 817.
55. Vanderpump MPJ. The epidemiology of thyroid disease. *Br Med Bull*. 2011; 99(1): 39–51.
56. Hollowell JG, Staehling NW, Dana Flanders W, Harry Hannon W, Gunter EW, Spencer CA, et al. Serum TSH, T(4), and thyroid antibodies in the United States population (1988 to 1994): National Health and Nutrition Examination Survey (NHANES III). *J Clin Endocrinol Metab*. 2002;87(2): 489–99.
57. Teng X, Shan Z, Chen Y, Lai Y, Yu J, Shan L, et al. More than adequate iodine intake may increase subclinical hypothyroidism and autoimmune thyroiditis: a cross-sectional study based on two Chinese communities with different iodine intake levels. *Eur J Endocrinol*. 2011; 164(6): 943–50.
58. Teng W, Shan Z, Teng X, Guan H, Li Y, Teng D, et al. Effect of iodine intake on thyroid diseases in China. *N Engl J Med*. 2000; 354(26): 2783–93.
59. Bjergved L, Jørgensen T, Perrild H, Carlé A, Cerqueira C, Krejbjerg A, et al. Predictors of change in serum TSH after iodine fortification: an 11-year follow-up to the DanThyr study. *J Clin Endocrinol Metab*. 2012; 97(11): 4022–9.
60. Caturegli P, de Remigis A, Chuang K, Dembele M, Iwama A, Iwama S. Hashimoto's thyroiditis: celebrating the centennial through the lens of the Johns Hopkins hospital surgical pathology records. *Thyroid*. 2010; 23(2): 142–50.
61. Li Y, Bai Y, Liu Z, Ozaki T, Taniguchi E, Mori I, et al. Immunohistochemistry of IgG4 can help subclassify Hashimoto's autoimmune thyroiditis. *Pathol Int*. 2009; 59(9): 636–41.
62. de Luca F, Santucci S, Corica D, Pitrolo E, Romeo M, Aversa T. Hashimoto's thyroiditis in childhood: presentation modes and evolution over time. *Ital J Pediatr*. 2013; 39.
63. Stagnaro-Green A. Approach to the patient with postpartum thyroiditis. *J Clin Endocrinol Metab*. 2012; 97(2): 334–42.
64. Konturek A, Barczyński M, Wierzchowski W, Stopa M, Nowak W. Coexistence of papillary thyroid cancer with Hashimoto thyroiditis. *Langenbeck's Archives of Surgery*. 2013; 398(3): 389.
65. Mandac JC, Chaudhry S, Sherman KE, Tomer Y. The clinical and physiological spectrum of interferon-alpha induced thyroiditis: toward a new classification. *Hepatology*. 2006; 43(4): 661–72.

66. Corsello SM, Barnabei A, Marchetti P, de Vecchis L, Salvatori R, Torino F. Endocrine side effects induced by immune checkpoint inhibitors. *J Clin Endocrinol Metab.* 2013; 98(4): 1361–75.
67. Vita R, Guarneri F, Agah R, Benvenga S. Autoimmune thyroid disease elicited by NY-ESO-1 vaccination. *Thyroid.* 2014; 24(2): 390–4.
68. Cárdenas-Roldán J, Rojas-Villarraga A, Anaya JM. How do autoimmune diseases cluster in families? A systematic review and meta-analysis. *BMC Med.* 2013; 11(1).
69. Vladutiu AO, Rose NR. Autoimmune murine thyroiditis relation to histocompatibility (H-2) type. *Science.* 1971; 174(4014): 1137–9.
70. Grumet FC, Coukell A, Bodmer JG, Bodmer WF, McDevitt HO. Histocompatibility (HL-A) antigens associated with systemic lupus erythematosus. A possible genetic predisposition to disease. *N Engl J Med.* 1971; 285(4): 193–6.
71. Simmonds MJ, Gough SCL. The search for the genetic contribution to autoimmune thyroid disease: the never ending story? *Brief Funct Genomics.* 2011; 10(2): 77–90.
72. Guaraldi F, Zang G, Dackiw AP, Caturegli P. Oncocytic mania: a review of oncocytic lesions throughout the body. *J Endocrinol Invest.* 2011; 34(5): 383–94.
73. Ahmed R, Al-Shaikh S, Akhtar M. Hashimoto Thyroiditis. *Advances in Anatomic Pathology.* 2021; 19(3): 181–6.
74. Makariou S, Liberopoulos EN, Elisaf M, Challa A. Novel roles of vitamin D in disease: what is new in 2011? *Eur J Intern Med.* 2011; 22(4): 355–62.
75. Bikle D. Nonclassic actions of vitamin D. *J Clin Endocrinol Metab.* 2009; 94(1): 26–34.
76. Prietl B, Treiber G, Pieber TR, Amrein K. Vitamin D and immune function. *Nutrients.* 2011; 5(7): 2502–21.
77. Lips P, Hosking D, Lippuner K, Norquist JM, Wehren L, Maalouf G, et al. The prevalence of vitamin D inadequacy amongst women with osteoporosis: an international epidemiological investigation. *J Intern Med.* 2006; 260(3): 245–54.
78. Lappe JM, Travers-Gustafson D, Davies KM, Recker RR, Heaney RP. Vitamin D and calcium supplementation reduces cancer risk: results of a randomized trial. *Am J Clin Nutr.* 2007; 85(6): 1586–91.
79. Stolzenberg-Solomon RZ, Vieth R, Azad A, Pietinen P, Taylor PR, Virtamo J, et al. A Prospective Nested Case-Control Study of Vitamin D Status and Pancreatic Cancer Risk in Male Smokers. *Cancer Research.* 2006; 66(20): 10213–9.
80. Stolzenberg-Solomon RZ, Hayes RB, Horst RL, Anderson KE, Hollis BW, Silverman DT. Serum Vitamin D and Risk of Pancreatic Cancer in the Prostate, Lung, Colorectal, and Ovarian Screening Trial. *Cancer Res.* 2009; 69(4): 1439.
81. Chlebowski RT, Johnson KC, Kooperberg C, Pettinger M, Wactawski-Wende J, Rohan T, et al. Calcium Plus Vitamin D Supplementation and the Risk of Breast Cancer. *JNCI Journal of the National Cancer Institute.* 2000; 100(22): 1581.
82. Vondra K, Stárka L, Hampl R. Vitamin D and thyroid diseases. *Physiol Res.* 2015; 64(Suppl 2): S95–100.
83. Holick MF. Vitamin D deficiency. *N Engl J Med.* 2007; 357(3): 266–81.
84. Plum LA, Deluca HF. Vitamin D, disease and therapeutic opportunities. *Nat Rev Drug Discovery.* 2010; 9(12): 941–55.



85. Muscogiuri G, Tirabassi G, Bizzaro G, Orio F, Paschou SA, Vryonidou A, et al. Vitamin D and thyroid disease: to D or not to D? *Eur J Clin Nutr*. 2015; 69(3): 291–6.
86. Kmiec P, Sworzczak K. Vitamin D in thyroid disorders. *Exp Clin Endocrinol Diabetes*. 2015; 123(7): 386–93.
87. Klecha AJ, Barreiro Arcos ML, Frick L, Genaro AM, Cremaschi G. Immune-endocrine interactions in autoimmune thyroid diseases. *Neuroimmunomodulation*. 2008; 15(1): 68–75.
88. Fountoulakis S, Tsatsoulis A. On the pathogenesis of autoimmune thyroid disease: a unifying hypothesis. *Clin Endocrinol (Oxf)*. 2004; 60(4): 397–409.
89. D'Aurizio F, Villalta D, Metus P, Doretto P, Tozzoli R. Is vitamin D a player or not in the pathophysiology of autoimmune thyroid diseases? *Autoimmun Rev*. 2015; 14(5): 363–9.
90. Baeke F, Takiishi T, Korf H, Gysemans C, Mathieu C. Vitamin D: modulator of the immune system. *Curr Opin Pharmacol*. 2010; 10(4): 482–96.
91. Mathieu C, Adorini L. The coming of age of 1,25-dihydroxyvitamin D(3) analogs as immunomodulatory agents. *Trends Mol Med*. 2002; 8(4): 174–9.
92. Hewison M. An update on vitamin D and human immunity. *Clin Endocrinol (Oxf)*. 2012; 76(3): 315–25.
93. Ponikowski P, Kirwan BA, Anker SD, McDonagh T, Dorobantu M, Drozd J, et al. Ferric carboxymaltose for iron deficiency at discharge after acute heart failure: a multicentre, double-blind, randomised, controlled trial. *Lancet*. 2020; 396(10266): 1895–904.
94. Aisen P, Enns C, Wessling-Resnick M. Chemistry and biology of eukaryotic iron metabolism. *Int J Biochem Cell Biol*. 2001; 33(10): 940–59.
95. Lieu PT, Heiskala M, Peterson PA, Yang Y. The roles of iron in health and disease. *Mol Aspects Med*. 2001; 22(1–2): 1–87.
96. Quintero-Gutiérrez AG, González-Rosendo G, Sánchez-Muñoz J, Polo-Pozo J, Rodríguez-Jerez JJ. Bioavailability of heme iron in biscuit filling using piglets as an animal model for humans. *Int J Biol Sci*. 2008; 4(1): 58–62.
97. Guerinot ML. Microbial iron transport. *Annu Rev Microbiol*. 1994; 48: 743–72.
98. Askwith C, Kaplan J. Iron and copper transport in yeast and its relevance to human disease. *Trends Biochem Sci*. 1998; 23(4): 135–8.
99. Hurrell R, Egli I. Iron bioavailability and dietary reference values. *Am J Clin Nutr*. 2010; 91(5).
100. Monsen ER, Hallberg L, Layrisse M, Hegsted DM, Cook JD, Mertz W, et al. Estimation of available dietary iron. *Am J Clin Nutr*. 1978; 31(1): 134–41.
101. Zhang HY, Teng XC, Shan ZY, Wang ZJ, Li CY, Yu XH, et al. Association between iron deficiency and prevalence of thyroid autoimmunity in pregnant and non-pregnant women of childbearing age: a cross-sectional study. *Chin Med J (Engl)*. 2019; 132(18): 2143–9.
102. He L, Shen C, Zhang Y, Chen Z, Ding H, Liu J, et al. Evaluation of serum ferritin and thyroid function in the second trimester of pregnancy. *Endocr J [Internet]*. 2018 [cited 2022 Apr 12]; 65(1): 75–82. Available from: <https://pubmed.ncbi.nlm.nih.gov/29033409/>

103. Hess SY, Zimmermann MB, Arnold M, Langhans W, Hurrell RF. Iron deficiency anemia reduces thyroid peroxidase activity in rats. *J Nutr.* 2002; 132(7): 1951–5.
104. Surks MI. Effect of thyrotropin on thyroidal iodine metabolism during hypoxia. *Am J Physiol.* 1969; 216(2): 436–9.
105. Eftekhari MH, Simondon KB, Jalali M, Keshavarz SA, Elguero E, Eshraghian MR, et al. Effects of administration of iron, iodine and simultaneous iron-plus-iodine on the thyroid hormone profile in iron-deficient adolescent Iranian girls. *European Journal of Clinical Nutrition.* 2006; 60(4): 545–52.
106. Khatiwada S, Gelal B, Baral N, Lamsal M. Association between iron status and thyroid function in Nepalese children. *Thyroid Research.* 2016; 9(1).
107. Okuroglu N, Ozturk A, Özdemir A. Is Iron Deficiency A Risk Factor for The Development of Thyroid Autoantibodies In Euthyroid Women With Reproductive Ages? *Acta Endocrinologica (Bucharest).* 2020; 16(1): 49.
108. Zhang HY, Teng XC, Shan ZY, Wang ZJ, Li CY, Yu XH, et al. Association between iron deficiency and prevalence of thyroid autoimmunity in pregnant and non-pregnant women of childbearing age: a cross-sectional study. *Chinese Medical Journal.* 2019; 132(18): 2143.
109. Veltri F, Decaillet S, Kleynen P, Grabczan L, Belhomme J, Rozenberg S, et al. Prevalence of thyroid autoimmunity and dysfunction in women with iron deficiency during early pregnancy: is it altered? *Clinical Study. European Journal of Endocrinology.* 2016; 175: 191–9.
110. Li S, Gao X, Wei Y, Zhu G, Yang C. The Relationship between Iron Deficiency and Thyroid Function in Chinese Women during Early Pregnancy. *J Nutr Sci Vitaminol (Tokyo).* 2016; 62(6): 397–401.
111. Brigham DE, Beard JL. Effect of thyroid hormone replacement in iron-deficient rats. *Am J Physiol.* 1995; 269(5 Pt 2).
112. Andersson M, Thankachan P, Muthayya S, Goud RB, Kurpad A v., Hurrell RF, et al. Dual fortification of salt with iodine and iron: a randomized, double-blind, controlled trial of micronized ferric pyrophosphate and encapsulated ferrous fumarate in southern India. *Am J Clin Nutr.* 2002; 88(5): 1378–87.
113. Hess SY, Zimmermann MB, Arnold M, Langhans W, Hurrell RF. Iron Deficiency Anemia Reduces Thyroid Peroxidase Activity in Rats. *The Journal of Nutrition.* 2002; 132(7): 1951–5.
114. McDermott MT, Ridgway EC. Central hyperthyroidism. *Endocrinol Metab Clin North Am.* 1998; 27(1): 187–203.
115. Hosny SS, Aboromia MMM, Ibrahim NA, Abd DK, Halim E, Ibrahim NA. The relationship between vitamin D level and thyroid antibodies in primary hypothyroidism. *The Egyptian Journal of Internal Medicine.* 2019; 31: 164–70.
116. Kaan Demircioglu M, Gul Demircioglu Z, Aygun N, Yilmaz Ozguven B, Ethem Akgun I, Uludag M, et al. Is Vitamin D Deficiency Associated with Chronic Lymphocytic Thyroiditis? *The Medical Bulletin Of Sisli Etfal Hospital Original Research. Med Bull Sisli Etfal Hosp.* 2021; 55(4): 510–5.
117. Krátký J, Ježková J, Kosák M, Vítková H, Bartáková J, Mráz M, et al. Positive Anti-thyroid Antibodies and Nonsuppressed TSH Are Associated with Thyroid Cancer: A Retrospective Cross-Sectional Study. *International Journal of Endocrinology.* 2018.

118. Yuan S, Li Q, Zhang Y, Huang C, Wu H, Li Y, et al. Changes in Anti-Thyroglobulin IgG Glycosylation Patterns in Hashimoto's Thyroiditis Patients. *The Journal of Clinical Endocrinology & Metabolism*. 2015; 100(2): 717–24.
119. Siriwardhane T, Krishna K, Ranganathan V, Jayaraman V, Wang T, Bei K, et al. Significance of Anti-TPO as an Early Predictive Marker in Thyroid Disease. 2019.
120. Mehanathan PB, Erusan RR, Shantaraman K, Kannan SM. Antithyroid Peroxidase Antibodies in Multinodular Hashimoto's Thyroiditis Indicate a Variant Etiology. *Journal of Thyroid Research*. 2019.
121. Chen CR, Hamidi S, Braley-Mullen H, Nagayama Y, Bresee C, Aliesky HA, et al. Antibodies to thyroid peroxidase arise spontaneously with age in NOD.H-2h4 mice and appear after thyroglobulin antibodies. *Endocrinology*. 2010; 151(9): 4583–93.
122. Hutfless SM, Matos P, Talor M v., Caturegli P, Rose NR. Significance of prediagnostic thyroid antibodies in women with autoimmune thyroid disease. *J Clin Endocrinol Metab*. 2011 Sep; 96(9).
123. Carlé A, Laurberg P, Knudsen N, Perrild H, Ovesen L, Rasmussen LB, et al. Thyroid peroxidase and thyroglobulin auto-antibodies in patients with newly diagnosed overt hypothyroidism. *Autoimmunity*. 2006; 39(6): 497–503.
124. Palacios C, Gonzalez L. Is vitamin D deficiency a major global public health problem? *J Steroid Biochem Mol Biol*. 2014; 144PA (PART A): 138.
125. Borges Botelho IM, Neto AM, Silva A, Tambascia MA, Alegre SM, Zantut-Wittmann DE. Vitamin D in Hashimoto's thyroiditis and its relationship with thyroid function and inflammatory status. Vol. 65. 2018.
126. Ahmed SS, Mohammed AA. Effects of thyroid dysfunction on hematological parameters: Case controlled study. *Annals of Medicine and Surgery*. 2020 Sep 1; 57: 52–5.
127. Rostaei Rad N, Vakili M, Zavar-reza J, Rezaie S, Reza Shirvani A. The Relationship between Thyroid Hormone Levels and Body Iron Status in Iranian Hypothyroidism Patients. *International Journal of Medical Laboratory*. 2016; 3(3): 176–84.
128. Dorgalaleh A, Mahmoodi M, Varmaghani B, node FK, Kia OS, Alizadeh S, et al. Effect of Thyroid Dysfunctions on Blood Cell Count and Red Blood Cell Indice. *Iranian Journal of Pediatric Hematology and Oncology*. 2013; 3(2): 73.
129. Tienboon P, Unachak K. Iron deficiency anaemia in childhood and thyroid function. *Asia Pacific J Clin Nutr*. 2003; 12(2): 198–202.
130. Martinez-Torres C, Cubeddu L, Dillmann E. Effect of exposure to low temperature on normal and iron-deficient subjects. *American Journal of Physiology - Regulatory Integrative and Comparative Physiology*. 1984; 15(3).
131. Ravanbod M, Asadipooya K, Kalantarhormozi M, Nabipour I, Omrani GR. Treatment of Iron-deficiency Anemia in Patients with Subclinical Hypothyroidism. *The American Journal of Medicine*. 2013; 126(5): 420–4.
132. Mehmet E, Aybike K, Ganidagli S, Mustafa K. Characteristics of anemia in subclinical and overt hypothyroid patients. *Endocr J*. 2012; 59(3): 213–20.
133. Das C, Sahana P, Sengupta N, Giri D, Roy M, Mukhopadhyay P. Etiology of anemia in primary hypothyroid subjects in a tertiary care center in Eastern India. *Indian J Endocrinol Metab*. 2012; 16(Suppl 2): 361.

134. Soliman AT, de Sanctis V, Yassin M, Wagdy M, Soliman N. Chronic anemia and thyroid function. *Acta Bio Medica : Atenei Parmensis*. 2017; 88(1): 119.
135. Chen SCH, Shirazi MRS, Orr RA. Triiodothyronine (T3) and thyroxine (T4) levels in iron-deficient, hypertriglyceridemic rats. *Nutrition Research*. 1983; 3(1): 91–106.
136. Beard J, Green W, Miller L, Finch C. Effect of iron-deficiency anemia on hormone levels and thermoregulation during cold exposure. <https://doi.org/10.1152/ajpregu.1984.247.1.R114>. 1986; 16(1).
137. Brigham DE, Beard JL. Effect of thyroid hormone replacement in iron-deficient rats. <https://doi.org/10.1152/ajpregu.1995.269.5.R1140>. 1995; 269(5): 38–5.
138. Beard JL, Borel MJ, Derr J. Impaired thermoregulation and thyroid function in iron-deficiency anemia. *Am J Clin Nutr*. 1990; 52(5): 813–9.
139. Azizi F, Mirmiran P, Sheikholeslam R, Hedayati M, Rastmanesh R. The relation between serum ferritin and goiter, urinary iodine and thyroid hormone concentration. *International journal for vitamin and nutrition research Internationale Zeitschrift für Vitamin- und Ernährungsforschung Journal international de vitaminologie et de nutrition*. 2002; 72(5): 296–9.
140. Zimmermann M, Adou P, Torresani T, Zeder C, Hurrell R. Iron supplementation in goitrous, iron-deficient children improves their response to oral iodized oil. *Eur J Endocrinol*. 2000; 142(3): 217–23.
141. Hess SY, Zimmermann MB, Adou P, Torresani T, Hurrell RF. Treatment of iron deficiency in goitrous children improves the efficacy of iodized salt in Côte d'Ivoire. *Am J Clin Nutr*. 2002; 75(4): 743–8.
142. Fu J, Yang A, Zhao J, Zhu Y, Gu Y, Xu Y, et al. The relationship between iron level and thyroid function during the first trimester of pregnancy: A cross-sectional study in Wuxi, China. *J Trace Elem Med Biol*. 2017; 43: 148–52.
143. Veltri F, Decaillat S, Kleynen P, Grabeczan L, Belhomme J, Rozenberg S, et al. Prevalence of thyroid autoimmunity and dysfunction in women with iron deficiency during early pregnancy: is it altered? *Eur J Endocrinol*. 2016; 175(3): 191–9.
144. Yu X, Shan Z, Li C, Mao J, Wang W, Xie X, et al. Iron deficiency, an independent risk factor for isolated hypothyroxinemia in pregnant and nonpregnant women of childbearing age in China. *J Clin Endocrinol Metab*. 2015; 100(4): 1594–601.
145. Zimmermann MB, Burgi H, Hurrell RF. Iron deficiency predicts poor maternal thyroid status during pregnancy. *J Clin Endocrinol Metab*. 2007; 92(9): 3436–40.
146. O'Kane SM, Mulhern MS, Pourshahidi LK, Strain JJ, Yeates AJ. Micronutrients, iodine status and concentrations of thyroid hormones: a systematic review. *Nutr Rev*. 2018; 76(6): 418–31.
147. Zimmermann MB. Iodine deficiency in industrialized countries. *Clin Endocrinol (Oxf)*. 2011; 75(3): 287–8.
148. Talaei A, Ghorbani F, Asemi Z. The Effects of Vitamin D Supplementation on Thyroid Function in Hypothyroid Patients: A Randomized, Double-blind, Placebo-controlled Trial. *Indian Journal of Endocrinology and Metabolism*. 2018; 22(5): 584.
149. Tamer G, Arik S, Tamer I, Coksert D. Relative vitamin D insufficiency in Hashimoto's thyroiditis. *Thyroid*. 2011; 21(8): 891–6.

150. Meng S, He ST, Jiang WJ, Xiao L, Li DF, Xu J, et al. Genetic susceptibility to autoimmune thyroid diseases in a Chinese Han population: Role of vitamin D receptor gene polymorphisms. *Ann Endocrinol (Paris)*. 2015; 76(6): 684–9.
151. Feng M, Li H, Chen SF, Li WF, Zhang F bin. Polymorphisms in the vitamin D receptor gene and risk of autoimmune thyroid diseases: a meta-analysis. *Endocrine*. 2013; 43(2): 318–26.
152. Mansournia N, Mansournia MA, Saeedi S, Dehghan J. The association between serum 25OHD levels and hypothyroid Hashimoto's thyroiditis. *J Endocrinol Invest*. 2014; 37(5): 473–6.
153. Zhang Y, Huang X, Chen Z, Yang Q, Li X, Zhang R, et al. Iron deficiency, a risk factor for thyroid autoimmunity during second trimester of pregnancy in China. *Endocrine Practice*. 2020 Jun 1; 26(6): 595–603.
154. Veltri F, Decaillet S, Kleynen P, Grabczan L, Belhomme J, Rozenberg S, et al. Prevalence of thyroid autoimmunity and dysfunction in women with iron deficiency during early pregnancy: is it altered? Clinical Study. *European Journal of Endocrinology*. 2016; 175: 191–9.
155. Sategna-Guidetti C, Bruno M, Mazza E, Carlino A, Predebon S, Tagliabue M, et al. Autoimmune thyroid diseases and coeliac disease. *Eur J Gastroenterol Hepatol*. 1998; 10(11): 927–31.
156. Fisher AH, Lomasky SJ, Fisher MJ, Oppenheim YL. Celiac disease and the endocrinologist: a diagnostic opportunity. *Endocr Pract*. 2008; 14(3): 381–8.
157. Pinto-Sánchez MI, Bercik P, Verdu EF, Bai JC. Extraintestinal manifestations of celiac disease. *Dig Dis*. 2015; 33(2): 147–54.
158. Tozzoli R, Kodermaz G, Perosa AR, Tampoia M, Zucano A, Antico A, et al. Autoantibodies to parietal cells as predictors of atrophic body gastritis: a five-year prospective study in patients with autoimmune thyroid diseases. *Autoimmun Rev*. 2010; 10(2): 80–3.
159. Lahner E, Centanni M, Agnello G, Gargano L, Vannella L, Iannoni C, et al. Occurrence and risk factors for autoimmune thyroid disease in patients with atrophic body gastritis. *Am J Med [Internet]*. 2008; 121(2): 136–41.
160. Checchi S, Montanaro A, Ciuoli C, Brusco L, Pasqui L, Fioravanti C, et al. Prevalence of parietal cell antibodies in a large cohort of patients with autoimmune thyroiditis. *Thyroid*. 2010; 20(12): 1385–9.
161. Centanni M, Marignani M, Gargano L, Corleto VD, Casini A, Delle Fave G, et al. Atrophic body gastritis in patients with autoimmune thyroid disease: an underdiagnosed association. *Arch Intern Med*. 1999; 159(15): 1726–30.
162. Szczepanek-Parulska E, Hernik A, Ruchała M. Anemia in thyroid diseases. *Pol Arch Intern Med*. 2017; 127(5): 352–60.
163. Zhang HY, Teng XC, Shan ZY, Wang ZJ, Li CY, Yu XH, et al. Association between iron deficiency and prevalence of thyroid autoimmunity in pregnant and non-pregnant women of childbearing age: A cross-sectional study. *Chinese Medical Journal*. 2019; 132(18): 2143–9.
164. Kivity S, Agmon-Levin N, Zisappl M, Shapira Y, Nagy E v., Dankó K, et al. Vitamin D and autoimmune thyroid diseases. *Cell Mol Immunol*. 2011; 8(3): 243–7.

165. D'Aurizio F, Villalta D, Metus P, Doretto P, Tozzoli R. Is vitamin D a player or not in the pathophysiology of autoimmune thyroid diseases? *Autoimmunity Reviews*. 2015; 14(5): 363–9.
166. Effraimidis G, Badenhoop K, Tijssen JGP, Wiersinga WM. Vitamin D deficiency is not associated with early stages of thyroid autoimmunity. *European Journal of Endocrinology*; 167(1): 43–8.
167. Choi YM, Kim WG, Kim TY, Bae SJ, Kim HK, Jang EK, et al. Low levels of serum vitamin D3 are associated with autoimmune thyroid disease in pre-menopausal women. *Thyroid*. 2014; 24(4): 655–61.
168. Kim CY, Lee YJ, Choi JH, Lee SY, Lee HY, Jeong DH, et al. The Association between Low Vitamin D Status and Autoimmune Thyroid Disease in Korean Premenopausal Women: The 6th Korea National Health and Nutrition Examination Survey, 2013–2014. *Korean Journal of Family Medicine*. 2019; 40(5): 323–8.