

Thyroid autoimmunity role of thyroid in antibodies in thyroid and extra thyroidal diseases

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Abstract- Autoimmune thyroid disease (AITD) refers to a spectrum of various diseases, with two extremes of clinical presentation, hypothyroidism (Hashimoto's thyroiditis (HT) and hyperthyroidism (Graves-Basedow disease (GBD)). Both conditions are characterized by presenting a cellular and humoral autoimmune reaction, with an increase in the synthesis and secretion of antibodies directed toward various thyroid antigens, together with a phenomenon of thyrocyte necrosis and apoptosis (in HT) and a persistent thyrotropin-receptor stimulation (in GBD). The diagnosis of both entities is based on clinical, laboratory, and imaging findings. Three major anti-thyroid antibodies have been described, those directed against the TSH receptor (TRAb), against thyroid peroxidase (TPOAb), and against thyroglobulin (TgAb). Each of these autoantibodies plays a fundamental role in the diagnostic approach of autoimmune thyroid disease. TRAbs are the hallmark of GBD, and additionally, they are predictors of response to disease treatment, among other utilities. Likewise, TPOAb and TgAb allow for identifying individuals with a higher risk of progression to hypothyroidism; the positivity of one or both autoantibodies defines the presence of thyroid autoimmunity. In this review, the usefulness of anti-thyroid antibodies in the diagnostic approach to autoimmune thyroid disease is described.

Keywords: Thyroid; autoimmunity; antibodies; thyrotropin; receptor; thyroglobulin; peroxidase.

I. INTRODUCTION

Autoimmune diseases (AD) represent a spectrum of disorders caused by inflammation of organs due to production of antibodies against self-structures and cytotoxic action of T cells. Data from Europe, North America, Australia, New Zealand (defined as area 1) and Asia, Middle East, Caribbean, South America (defined as area 2) differ in the reported prevalence (cases/100,000 individuals) of the most frequent AD as follows: Graves' disease (GD, area 1: 50–626, area 2: 20), Hashimoto's thyroiditis (HT, chronic autoimmune thyroiditis, autoimmune hypothyroidism, area 1: 300–2,980, area 2: 350), rheumatoid arthritis (RA, area 1: 310–810, area 2: 120–550), type 1 diabetes mellitus (T1DM, area 1: 310–570, area 2: no data), Crohn's disease (CRD, area 1: 28–201, area 2: 6–113), multiple sclerosis (MS, area 1: 177–358, area 2: 4–101), and Sjögren disease (SD, area 1: 93–3,500, area 2: 330–1,560). The disparity by sex is high in most of these diseases with a female preponderance of $\geq 85\%$; only in some childhood-onset AD, such as T1DM, is the risk equal in both sexes. There are three age peaks for AD onset, namely, 8–10 years (juvenile RA, T1DM), 33–50 years (myasthenia gravis, MS, systemic lupus erythematosus, scleroderma, GD), and 52–63 years (HT, SD, adult RA, etc.). Autoimmune thyroid diseases (AITDs) include several inflammatory thyroid diseases with GD and HT as most frequent forms.

II. FACTORS LINKED TO THYROID AUTOIMMUNITY

Autoimmune thyroid diseases are usually accompanied by the presence of anti-thyroid peroxidase (TPO), anti-thyroglobulin (Tg), and anti-thyroid-stimulating hormone receptor (TSHR) antibodies. Antibodies against thyroid antigens such as carbonic anhydrase 2, megalin, T3 and T4, sodium iodide symporter (NIS), and pendrin have also been detected¹⁻³.

III. Thyroid-Stimulating Hormone Receptor

After expression on the thyrocyte cell surface, the TSHR undergoes cleavage within the "hinge" region at two or more sites; loss of a C-peptide like region leads to an extracellular A-subunit linked by disulfide bonds to the B-subunit (comprising the remainder of the hinge region, transmembrane, and cytoplasmic tail). Subsequently, some A-subunits are shed. Substantial evidence suggests that the shed A-subunit (rather than the holoreceptor) is the autoantigen initiating and/or driving the autoimmune response to the TSHR in GD. As shown by crystallization, stimulating TSHR monoclonal antibody M22 and TSH blocking monoclonal antibody K1-70 (both of human origin) bind to closely overlapping epitopes at the amino terminus. In addition, neutral antibodies directed against the "hinge"

region exist. These antibodies can induce generation of oxidative radicals and induce apoptosis. The balance between stimulating TSHR and neutral antibodies can provide a balance between thyrocyte proliferation and apoptosis. DNA released from apoptotic cells stimulates the immune response. Since shedding of A-subunits occurs in all humans, the presence of exogenous and endogenous factors (see Environmental (Exogenous) Factors and Endogenous Factors) is mandatory for the development of GD. The biological action of autoantibodies against TSHR was the reason for their discovery by Adams and Purves . These authors were the first to identify a molecule with similar action to TSH and termed it long-acting thyroid stimulator (LATS) due to its prolonged effect. LATS was later identified as an immunoglobulin G and later found to be an antibody against TSHR. Anti-TSHR antibodies are found in 90% of GD patients, 0–20% HT, and 10–75% of atrophic thyroiditis patients. Other studies noted TSHR antibodies in around 10% of HT patients. Stimulating antibodies can be oligoclonal and belong to IgG1 class, while blocking antibodies are polyclonal and not restricted to a specific subclass . The pleiotropic action of anti-thyroid antibodies is typical for anti-TSHR antibodies. Stimulatory antibodies are detected in 73–100% and blocking anti-TSHR antibodies in 25–75% of GD patients. The variations in the detection appear to be linked to the type of assay that has been used. TRAb usually refers to any type of antibody interacting specifically with the TSHR. When assessed by competitive binding assay, the TSHR antibodies are called TSHR-binding inhibitory immunoglobulins. By contrast, cellbased bioassays measure either TSHR stimulatory antibodies or TSHR-stimulating immunoglobulins, or alternately TSHR blocking antibodies (TBAb) or TSHR-blocking immunoglobulins. Although all studies support the higher prevalence of stimulatory antibodies, the presence of only blocking TSHR antibodies may cause myxedema . High TSHR antibodies at diagnosis and/or positive TSHR antibodies at cessation of therapy suggest a high likelihood of relapse, mostly within the first 2 years. The levels can help to identify patients that need definitive therapy (radioiodine or surgery) . Anti-TSHR antibodies can cross the placental barrier and may induce transient hyperthyroidism in the neonate . Since half-life of IgG is ~3 weeks, symptoms disappear gradually. Blocking antibodies may also cause transient hypothyroidism with delayed development of the neonate thyroid gland⁴.

IV. Thyroid Peroxidase

Thyroid peroxidase is a poorly glycosylated membrane-bound enzyme, responsible for iodine oxidation and iodination of tyrosyl residues of the Tg molecule . It had been termed microsomal antigen based on its intracellular localization. Antibodies react against conformational epitopes at the surface of the molecules and against linear epitopes. Polyclonal antibodies from healthy individuals and patients are directed against the same epitopes. Anti-TPO antibodies from healthy subjects did not block TPO activity or interfere with the blocking activity of anti-TPO antibodies from AITD patients, while anti-TPO antibodies from AITD patients can fix complement, destroy thyrocytes, and act as competitive inhibitors of enzymatic activity . These antibodies can be of any class of IgG, although some studies indicated a higher prevalence of IgG1 (70%) and IgG4 (66.1%) compared to IgG2 (35.1%) and IgG3 (19.6%) . Low levels of IgA antibodies have also been reported. Anti-TPO antibodies are more common than anti-Tg antibodies and more indicative for thyroid disease. Anti-TPO antibodies are inducers of oxidative stress evidenced by decreased antioxidant potential, advanced glycosylation products and oxygen metabolites in blood . However, their contribution to thyroid damage compared to T cell and cytokine-mediated apoptosis is minor . Anti-TPO antibodies are detected in 90–95% of AITD patients, 80% of GD, and 10–15% of non-AITD patients . While anti-TPO antibodies may act cytotoxic on thyrocytes in HT they do not have an established role in GD. Anti-TPO antibodies are able to cross the placenta barrier to variable extent, but the effect on the neonate is unclear. Concerns on a potential negative effect on cognitive development of the offspring have not been confirmed so far⁵.

V. Thyroglobulin

Thyroglobulin is a large (600 kDa) glycoprotein consisting of dimers and containing on average 2–3 molecules of T4 and 0.3 molecules T3. The molecule is heterogeneous regarding hormone content, glycosylation, and size. The production of antibodies against Tg can be induced by massive destruction of the thyroid gland, but high Tg levels in blood do not per se induce antibody production. Out of the 40 epitopes that have been identified, according to some authors and 1–2 according to others are immunogenic. Antibodies against Tg differ between healthy subjects and AITD patients in that polyclonal antibodies are seen in normal subjects and oligoclonal antibodies in AITD patients. Antibodies in healthy subjects and AITD patients differentially recognize mainly two conformational epitopes of the molecule . Pattern of anti-Tg antibodies are similar in GD and HT patients and similar in healthy individuals and patients with TC . In general, low levels of self-antigens induce tolerance. It has been hypothesized that normal blood levels of Tg induce self-tolerance in T cells but not in B cells. B cells that recognize Tg arrest their migration in the T cell zone of peripheral lymphoid tissues but do not interact with CD4 helper cells. The lack of interaction prevents the B cells from migrating out of the T cell zones into the follicles, and they undergo apoptosis. As a consequence of the B cell activity, healthy individuals have very low, usually below detection threshold levels of anti-Tg antibodies. In the presence of higher Tg levels after tissue damage, changed conformation of the Tg molecule due to high I2 levels, and supernormal TSH levels, the anti-Tg antibody titers become abnormal. Administration of I2 induced

antibody production in 8–20% of subjects, together with intra-thyroidal lymphocyte infiltration in some of the patients. The proposed mechanisms are either antibody formation due to massive release of antigens following thyrocyte destruction or generation of new epitopes by a changed and more immunogenic conformation of the Tg molecule with high I2 content. The effects of I2 on immune responses of Tg and TPO antigens in thyroid autoimmunity might not be completely the same. On the basis that salt intake is the main source of I2, universal salt iodization has been introduced as protective measure against goiter. Excessive I2 intake, defined as table salt I2 concentrations of 40–100 mg/kg for 5 years, increased thyroid autoimmunity. Anti-Tg antibodies do not fix complement because the epitopes are too widely spaced to allow cross-linking. Furthermore, anti-Tg antibodies in GD belong mainly to the IgG4 class, which is not complement binding. Low levels of IgA antibodies have also been reported. IgM antibodies against Tg have been reported to 1% in healthy individuals. The functional consequence of anti-Tg antibodies is not clear as they do not cause thyroid cell destruction. Circulating antibodies could be detected in about 10% of healthy young subjects and 15% of people >60 years of age. Among HT patients, antibody prevalence was 60–80% and in 50–60% in GD patients. Another study identified anti-Tg antibodies in 70–80% of AITD patients, 30–40% of GD patients, and 10–15% of patients with non-thyroid immune disorders. Anti-Tg antibodies can cross the placenta barrier, but the effect on the neonate is unclear. The distribution among the classes of antibodies against Tg has been reported differently. IgG1 and IgG4 were the most important classes in GD and HT patients according to one study, while other authors reported distribution between IgG1, IgG2, and IgG4 classes. Interestingly, distribution differed between GD and HT patients; IgG4 class was dominant in patients with GD and IgG2 class in HT patients. This different distribution may reflect the different type of immune action taking place in the thyroid⁶.

VI. Other Thyroid Antigens

Antibodies against other thyroid autoantigens are not determined routinely since their incidence is much lower and their physiological role unclear. Data obtained by immunization of mice and binding of patient sera to stably transfected COS 7 cells expressing high levels of NIS indicate that the antibodies did not display marked inhibiting effect on iodide uptake. Macro-TSH is the result of the binding of anti-TSH antibodies to TSH and results in a high-molecular protein complex with low TSH bioreactivity. Incidence increases with age, and altered TSH antigenicity or decrease in autoimmune tolerance have been proposed as pathogenic mechanism. In summary, prevalence of anti-TPO and anti-Tg antibodies is high in patients with GD and HT, while anti-TSHR antibodies are common in GD patients but relatively rare in patients with HT. This may suggest that anti-TSHR antibodies are produced under more specific situations than the other antibodies. This difference is also reflected in some factors that have opposite effects in GD and HT, like, for instance, smoking and stress. There are additional differences in development and manifestation of the diseases. GD is usually characterized by rapid onset of the symptoms and is, except for elderly people with less typical symptoms, diagnosed and treated quite fast. Established treatments normalize titers of TSHR antibodies in adults within 2 years, while treatment of children and adolescents requires longer treatment times. HT develops gradually over months and years with very high antibody titers in some patients. Symptoms can be mild, and patients might not seek medical advice. Even when treatment has been initiated, titers of anti-TPO antibodies decrease only slowly (e.g., over 5 years) upon treatment with levothyroxine, and anti-TPO antibody titers remain in the pathological range. Normal anti-thyroid antibody titers are lower for anti-TSHR antibodies than for anti-TPO and anti-Tg antibodies. Exact values cannot be compared directly since sensitivities of the assays differ, but the range of >1.75 U/ml for anti-TSHR, >35 U/l for anti-TPO, and >20 U/l for anti-Tg according to most laboratories can serve as approximate indication that titers are markedly different⁷.

VII. Environmental (Exogenous) Factors

Exogenous and endogenous factors contribute to the risk of developing AITDs. Major exogenous causative factors are infections, intake of particular substances, and radiation, while endogenous factors are mainly sex and genetic disposition (Figure 1).

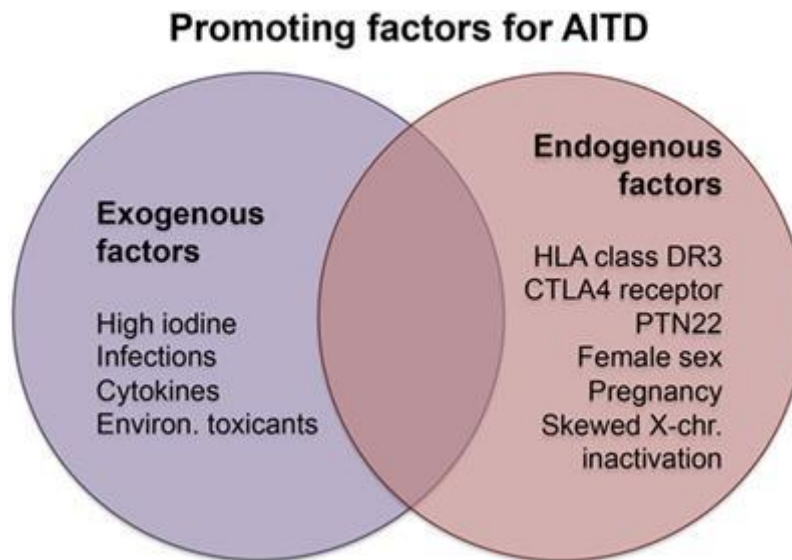


FIGURE 1 | Promoting factors in Hashimoto's and Graves' disease. Abbreviations: chr., chromosome; CTLA4, cytotoxic T-lymphocyte-associated protein 4; Environ., environmental; PTN22, protein tyrosine phosphatase, non-receptor type 22.

Factors with Opposite Effects on GD and HT Exogenous factors include smoking, which has a protective effect on HT incidence by lowering anti-Tg and anti-TPO antibody levels, while favoring the development of GD (odd's ratio, OR 3.3). Opposing effects in AD affecting the same organs have also been reported for inflammatory bowel diseases. Smoking protects against ulcerative colitis but induces worsening of CRD. Recent studies suggest that smoking acts through modulation of the phenotype of dendritic cells, which are involved in the activation and differentiation of T cells . It might be speculated that a similar mechanism also causes the different effect of smoking on HT and GD. Stress or major life events can increase the prevalence of GD, but not of HT⁸.

VIII. Protective Factors

Alcohol intake, which protects against several AD, also decreases the incidence of GD and of HT; abstainers have a 2.17 higher risk than non-abstainers . High doses of alcohol consumption can directly suppress immune responses, and alcohol abuse is associated with an increased incidence of a number of infectious diseases . Moderate alcohol consumption seems to have a beneficial impact on the immune system compared to alcohol abuse or abstinence, but the mechanisms behind the protective effect are not clear. Selenium supplementation does not consistently decrease anti-TPO antibody levels, which might be due to different baseline concentrations of both selenium and anti-TPO antibodies. Vitamin D supplementation has the reputation of improving immunological function, but studies on vitamin D in AITDs are not conclusive ; insufficient matching of all patients' parameters was suspected to potentially hide an existing correlatioproliferative response of the T cells, which might explain associations with AD. SNPs in the PTN22 gene enable efficient inhibition of T cell activation and impaired thymic deletion of autoreactive T cells in combination with inhibition of regulatory T cells. This was suggested as reason why this might lead to AD. Additional SNPs have been identified in Tg genes, the vitamin D receptor, IL-4, transforming growth factor-beta (TGF- β), FoxP3, and the tumor necrosis factor-alpha (TNF- α) gene. Genomic imprinting (the activation of maternal or paternal genes) has not been well studied in AD, but the Tg promoter appears to be a candidate for epigenetic effects (silencing or activation of genes) in AITDs. Female preponderance is seen in all AD. AITD is one example where this is very pronounced, and many studies aimed to understand the underlying mechanisms focusing first on differences in the immune system. Females have similar numbers of lymphocytes but higher antibody production by B cells. In addition to that, females have stronger humoral and cellular immune responses, higher CD4+ T cell levels after immunization, and lower susceptibility to various bacterial infections. Typically, only herpes simplex type 2 infections are more common in females than in males. One reason for the observed differences might be the prominent immune modulatory effects of estrogens. Immune cells carry receptors for estrogen, testosterone, and progesterone . Estrogen decreases the CD4+/CD8+ T cell ratio and TNF- α cytotoxicity in T cells and increases immunoglobulin secretion, B cell survival, and polyclonal activation of B cells as well as IgG and IgM production in peripheral blood mononuclear cells. High estrogen levels decrease Th1 pro-inflammatory pathways and increase Th2 anti-inflammatory pathways. Progesterone in general acts in an anti-inflammatory manner by inhibition of macrophage activation, nitric oxide production, and IFN- γ production by NK cells. The higher prevalence of AD in patients with structural X-chromosome defects and monosomy implied a crucial role of the X-chromosome in autoimmune reactions. In women, one of the two X-chromosomes is inactivated in every cell. Usually, the ratio of inactivation is

50:50 for paternal and maternal X-chromosomes. However, in some women a skewed inactivation is seen that could lead to insufficiently high levels of specific antigens to induce self-tolerance. Consistent with this idea skewed X-chromosome inactivation has been preferentially detected in women with AITD with a correlation of OR 2.54 for GD and 2.40 for HT. The correlation of skewed X-chromosome inactivation and TPO antibody level was stronger in dizygotic than in monozygotic twin supporting the assumption that the inactivation is more important for the manifestation of the disease than the genes themselves. The Y-chromosome is less important for survival because it harbors only a few genes. Nevertheless, loss of the Y-chromosome has been identified in GD and HT patients and is accompanied by reduced testosterone levels. The few genes not related to male fertility are X-chromosome homologs with relevant roles in immune function. The loss could cause haplo-insufficiency similar to X-chromosome loss, and an imbalance for the alleles shared with the X-chromosome could emerge. An additional reason might be the relationship between thyroid and testosterone via regulation of sex-hormone binding globulin. High thyroid hormone levels increase the levels of free testosterone with subsequent physiological effects. Alterations in hormone levels such as increases in testosterone in females with polycystic ovary syndrome increase the prevalence of AITDs. Pregnancy has a marked impact on AD, whereby the number of regulatory T cells is increased in gravidity and levels of antithyroid antibodies decreased. This decrease is usually transient, and a rebound effect of the antibody levels is seen 6 weeks postpartum. The postpartum period is a risk for onset of GD, and postpartum thyroiditis may lead to HT. Postpartum thyroiditis is defined as destructive thyroiditis within 1 year of parturition. The disease is characterized by transient hypothyroidism or hyperthyroidism or hyperthyroidism followed by hypothyroidism. Patients often recover, but there is up to a 50% risk of developing permanent thyroid disease with time. Previous pregnancy as a risk factor for AITD could be due to fetal microchimerism, i.e., the phenomenon that fetal cells and antigens are transferred to the mother. Fetal microchimeric cells have been found particularly in AITD patients. The fetal cells were cytotoxic T cells able to mitigate graft-versus-host reactions. The more fetal cells show similarities with the maternal cells, the more likely they have the potential to mediate such reactions. Although pregnancies ≥ 1 have an OR of 1.1–1.8 for AITD compared to nulliparous women there is still no proof for the hypothesis that fetal microchimerism causes HT. Furthermore, parity is not linked to increased antibody levels in all studies. Hashimoto's Thyroiditis Hashimoto's thyroiditis may lead to manifest hypothyroidism, but most patients have subclinical hypothyroidism with increased TSH and normal thyroid hormone levels. There are different variants of HT, termed fibrous, fibrous atrophic (Ord's disease), or goitrous forms, and IgG4 thyroiditis. Based on debates that Riedel thyroiditis is not primarily a thyroid disease but rather a manifestation of the systemic disorder multifocal fibrosclerosis, this variant is no longer classified as a variant of HT. Conversely, IgG4-related thyroiditis is now recognized as new entity of AITD. IgG4-related thyroiditis is associated with more frequent subclinical hypothyroidism and with higher levels of thyroid autoantibodies compared to the non-IgG4 thyroiditis group. In contrast to the other AITD forms there is a male preponderance. In long course of HT mainly IgG4 autoantibodies are produced, which trigger the development of IgG4-related disease (IgG4-RD). IgG4-RD can affect a variety of tissues (pancreas, skin, salivary glands, lacrimal glands, etc.), and the hallmarks are lymphoplasmacytic infiltrations with predominance of IgG4-positive plasma cells and fibrosis in the affected tissue. The atrophic form is more common than HT with enlargement of the thyroid gland. Although both forms lead to hypothyroidism, they have been reported as distinct diseases, differing in immunological background (associated with different HLA alleles), involvement of autoantibodies, and type of immune response (humoral versus cellular). The hypothesis that Ord's disease was the end stage of HT could not be confirmed in follow-up studies. Thyroid autoantibody levels differ between goitrous and atrophic thyroiditis in that inhibitory TSHR antibodies are higher in Ord's thyroiditis. These antibodies block cAMP production as well as TSH-induced DNA synthesis and iodide uptake. It has been hypothesized that antibody production promotes progression to hypothyroidism because higher levels of antibodies against Tg and TPO accompany deterioration of thyroid function. Destruction of the thyroid gland $>90\%$ leads to hypothyroidism. In the case of overt hypothyroidism, patients experience fatigue, weight gain, increased sensitivity to cold, difficulty concentrating, dry skin, nails, and hair, constipation, drowsiness, muscle soreness, and increased menstrual flow. HT is much more frequent in individuals affected by another AD. Although high anti-thyroid antibody titers may provide an indication of the likelihood of overt hypothyroidism, no correlation of antibody titer and risk for hypothyroidism has been found so far⁹.

IX. Graves' Disease

Symptoms often become manifest after emotional trauma and symptoms of hyperthyroidism arise with weight loss, weakness, dyspnea, palpitations, increased hunger and thirst, hyperdefecation, sweating, sensitivity to heat, tremor, irritability, and menstrual irregularity. Thyroid metabolism is accelerated with faster plasma turnover, higher TPO activity, excess Tg release, increased clearance of iodide from the plasma and decreased retention of iodide in the thyroid, and usually increased gland volume. Administration of high doses of I₂ (1–2 mg) temporarily inhibits iodide uptake, trapping, organification, and hormone release in addition to reduction of thyroidal blood flow. Organification of I₂ presumably is decreased by the blocking action of an oxidized iodide intermediate or depressed H₂O₂

generation. Although the blocking of I₂ organification, reduced iodide uptake, and hormone release is a physiological reaction of the thyroid (Wolff–Chaikoff effect), it is more pronounced in GD patients than in healthy controls¹⁰.

X. Anti-thyroid Antibodies in Extra-Thyroidal Pathologies

Anti-TSHR Antibodies Extra-thyroidal manifestation of GD include swelling of the orbital tissue and of the skin, termed as Graves' orbitopathy (GO) and Graves' dermopathy. The term ophthalmopathy is also being used, but orbitopathy is preferred because it describes the pathological alterations more correctly. GO affects about 25% of GD patients and results in dysmobility of extraocular muscles and optic nerve compression. It represents also the only extra-thyroidal pathology where the role of anti-thyroid antibodies is relatively well known. Target cells are infiltrating autoreactive T cells and fibroblasts resident between the extra-orbital muscles. These cell types interact via cytokine secretion and mutually stimulate each other. Both cell types express TSHR and IGF-1 receptors, which form a functional complex on orbital fibroblasts. Activated fibroblasts may either differentiate into myofibroblasts or adipocytes, or they may secrete hyaluronic acid and prostaglandin E₂. Major cytokines secreted by T cells include IL-1, IL-4, IL-6, TGF- β , leukoregulin, and IGF-1, while orbital fibroblasts release IL-1, IL-6, IL-8, IL-10, IL-12, MCP-1, and TNF- α . Inflammation and increased hyaluronic acid cause an increase in volume and lead to exophthalmos. Anti-TSHR antibody levels correlate with severity of GO and are predictive for the later development. By contrast, no correlation between severity of GO and hormone levels has been identified. This finding highlights the role of TSHR antibodies as promoters of GO. Graves' dermopathy is an extra-thyroidal manifestation exclusively found in GD patients. Dermopathy develops in the presence of high TSHR antibody levels and is, with a frequency of 15%, a less common extra-thyroidal manifestation of GD. The main localization is pretibial and is associated with acropachy (digital clubbing, swelling of digits and toes, and periosteal reaction of extremity bones) in 20% of patients. TSHR is expressed in skin fibroblasts and abundant mucin deposition, possessing gel-like properties, separates the collagen fibers. Stimulation of fibroblasts by anti-TSHR antibodies along with mechanical factors and venous stasis causes accumulation of mucin. Trauma and injury may lead to the activation of T cells and the initiation of an antigen specific response, in this case the activation of fibroblasts and production of glucosaminoglycans (GAGs)¹¹.

XI. Thyroid Antigens as AITD Susceptibility Genes TSHR gene:

Graves' disease results from the production of TSHR stimulating antibodies, which activate elevated thyroid hormone synthesis and secretion, leading to clinical thyrotoxicosis. TSHR antibodies are present in all patients of GD, and the disease severity directly correlates with blood TSHR antibody levels. Besides this, injecting animals with TSHR antibodies transfers disease, and transfer of antibodies from mothers with GD to newborns also transfers GD. The completion of the Human Genome Project along with the discovery of dense maps of single nucleotide polymorphisms (SNPs) revealed that the TSHR gene is strongly associated with GD and that most of the causative SNPs are located within intron. Reduction of TSHR expression because of the SNPs in the thymus, enables TSHR targeting autoreactive T cells to escape deletion in the thymus and leads to disease later in life (Figure 2).

Thyroglobulin gene: Inasmuch as Tg constitutes ~80% of total thyroid content, and as Tg can leak into the circulation and is exposed to the immune system, Tg is an important candidate gene for AITD. Besides, the best model of human autoimmune thyroiditis is induced by immunizing mice with Tg, as Tg may be the earliest disease trigger. That Tg may be an AITD susceptibility gene came from linkage studies showing a significant linkage peak on chromosome 8q at the Tg gene region. Sequencing of the Tg gene identified amino acid variants that are significantly associated with AITD and one such SNP in exon, showed significant statistical interaction with a human leukocyte antigen (HLA)-DR variant containing an arginine at position β 74 (HLA-DR β 1-Arg74), together conferring a high risk for AITD. However, a direct link between the Tg SNPs and the pathogenic Tg peptides is not yet established¹².

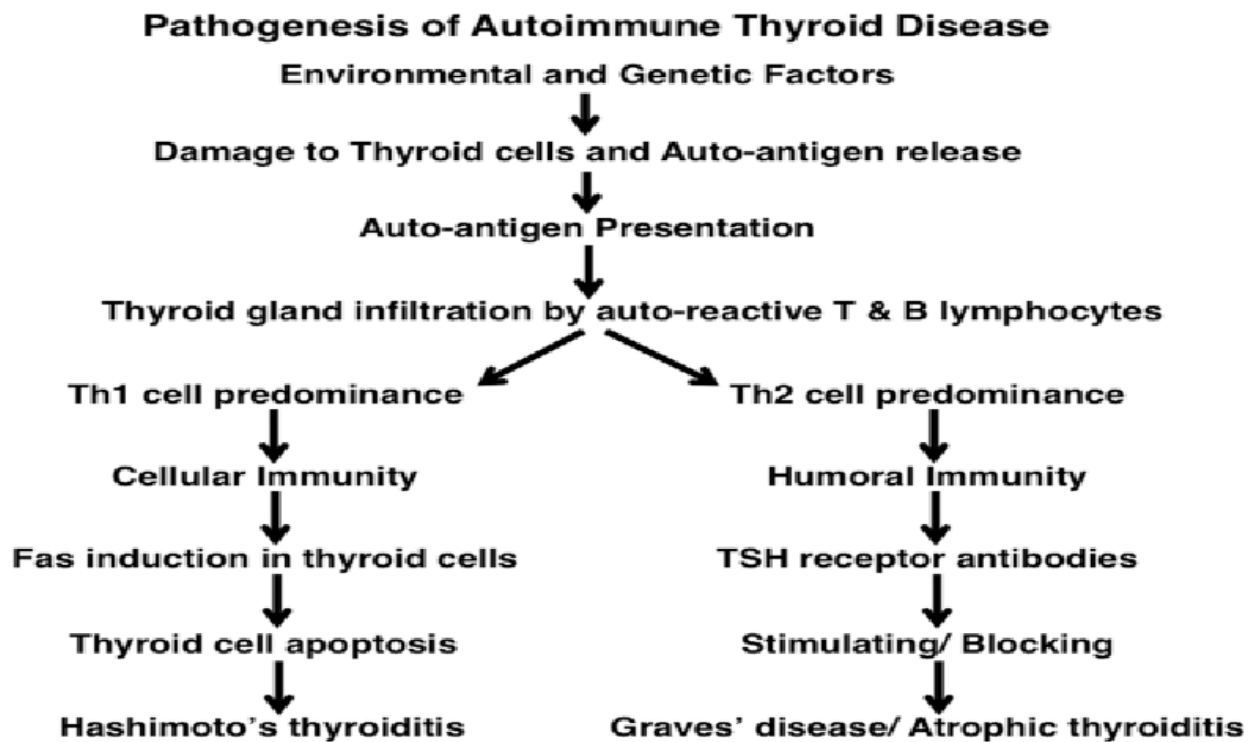


Fig 2 :- Flow-chart of events involved in the pathogenesis of autoimmune thyroid disease

Immune response genes as AITD susceptibility genes: Genetic screens identified HLA locus as the first such association with both GD and HT59 and in particular, HLA-DR3 was found to confer the strongest risk of all GD susceptibility genes identified and also to predispose for HT. As mentioned above, presence of arginine at position 74 of the HLA-DR β -chain is essential for the development of AITD, and a substitution mutation of this arginine residue with glutamine is protective from AITD60. Another important immune response AITD susceptibility gene is CD40, which plays a key role in the cross talk between antigen-presenting cells (APCs) and T cells. CD40 normally provides a crucial signal for proliferating, differentiating, and switching to the production of immunoglobulin G in B-lymphocytes61. Because of its role in B-cell function, and as GD is a B cell mediated autoimmune disease, CD40 is a unique GD susceptibility gene61,62. Upregulation of CD40 by SNP, rs1883832, can effectively lower the threshold for B cell activation leading to the onset of autoimmune disease. Activation of CD40 in thyrocytes has been shown to enhance cytokine (e.g., IL6) secretion followed by the activation of resident T cells, leading to a local inflammatory response and autoimmunity and both these mechanisms contribute to GD61,62. Besides HLA-DR and CD40, three other genes involved in T cell activation and regulation Figures 1 and 2 are found to be associated with AITD, viz., cytotoxic T lymphocyte-associated antigen 4 (CTLA-4), protein tyrosine phosphatase nonreceptor type 22 (PTPN22), and CD255. While several polymorphisms in the CTLA-4 gene were known to be associated with Besides HLA-DR and CD40, three other genes involved in T cell activation and regulation Fig 2 is found to be associated with AITD, viz., cytotoxic T lymphocyte-associated antigen 4 (CTLA-4), protein tyrosine phosphatase nonreceptor type 22 (PTPN22), and CD255. While several polymorphisms in the CTLA-4 gene were known to be associated with AITD65. Also, CD25 gene, which encodes for interleukin-2 receptor α -chain (IL-2R α) is associated with GD66. In the first genome-wide association study of GD conducted in China, 1,536 GD patients and 1,516 control subjects were genotyped for approximately 660,000 SNPs67. In this mega study, the investigators confirmed many of the previously identified GD loci, and also mapped on chromosomes 6q27 and 4p14, two new GD loci, which contain several genes; however, the identity of GD conferring gene(s) in these loci is still unclear¹³.

XII. Conclusion

AITD, which is of two types, Graves' disease and Hashimoto's disease, has much higher prevalence among women than in men and this in part related to pregnancy. Predominantly, autoimmune reaction against thyroid gland proteins, thyroglobulin, TPO and TSHR triggers AITD. As expected, AITD incidence is influenced significantly by geographical, environmental and genetic factors and also ageing. Recent advances in genome-wide association studies (GWAS) identified many SNPs in gene loci that are strongly associated with AITD, even though the precise cause and effect relationship between specific gene function and the disease have not been defined.

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