Chapter

Autoimmune Mechanism and Recurrence Risk in Graves' Disease

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Abstract

Graves' Disease (GD) is an autoimmune thyroid disorder where autoantibodies are produced against TSH (Thyroid Stimulating Hormone) receptor causing thyrotoxicosis. It is characterized by goiter, ophthalmopathy, and occasionally pretibial myxedema. The autoimmune mechanism causing disease is not well understood and it is complex. It involves multifactorial etiology involving environmental and genetic factors. Smoking and positive family history contributing to the development of GD. GD can be diagnosed based on the clinical manifestation and demonstrating low concentration of TSHs, high TRab (Thyroid Stimulating Hormone receptor autoantibodies), and high FT4 (Free thyroxine) concentration. Current treatment options aimed at stable restoration of euthyroidism by following different modalities of suppressing thyroid gland using antithyroid drugs, removing/ablating thyroid gland by surgery, and radioactive iodine treatment with iodine- 131.

Keywords: Graves' Disease, Thyroid Stimulating Hormone, Thyroid Stimulating Hormone receptor autoantibodies, Free thyroxine

1. Introduction

In this particular, Graves' Disease (GD) an autoimmune disorder, caused by excessive secretion of the glandular thyroid hormones by the thyroid follicles, which is related to the progressive hyperthyroidism condition. It is found to be the main cause of hyperthyroidism. The annual incidence has been reported of about 14–50 cases per 100,000 populations [1]. The disease may affect at any age and the incidence increases with age. The peak incidence of GD is between 30 and 50 years. It is generally accepted that younger patients have a severe immune system disorder where GD is predominantly found [1]. Few studies showed that younger patients are having poorer responses to ATD and poor prognosis with recurrent risk [2–4]. The lifetime risk of getting Graves' Disease is roughly 6 times higher in women than in men [1]. The exact mechanism of affecting the different gender is not known but believed to be associated with different sex hormones. Females are being affected more and the strongest risk factor contributed to the development of GD is estrogen. Estrogen influences B- cell functioning and regulates the immune system [5]. In GD patients, elevated estradiol relates to TRAb (TSH receptor antibody) positivity [6]. The risk of recurrence of GD after the withdrawal of the anti-thyroid drugs (ATG) is majorly seen in male GD patients [7, 8]. Large goiter with severe immune disorders and genetic aspects are associated with the development of GD in males. Genetic factors associated with GD are cytotoxic T-associated lymphocyte factor-4 (CTLA4) rs231779 and rs231775, especially Thyroglobulin (Tg) and TSHR

polymorphisms are linked with relapse in GD after the withdrawal of ATD. At four weeks following the completion of a randomized tobacco trial of ATD, the TRAb level was significantly higher in smokers than in nonsmokers [9–11]. Smoking promotes elevated levels of TRAb contributed to the development of GD. A number of factors recognized against GD includes stress, sex and sex hormones, pregnancy, infection, other autoimmune diseases, iodine and other potential environmental factors such as radiation have been recognized against Graves' Disease. The resulting breakdown in thyroid tolerance would lead to errors in multiple protective immune mechanisms. It is noted that sera of Graves's patients may contain the "predominant Hashimoto" thyroglobulin (Tg) and thyroid peroxidase antibodies (TPO Abs). Antibodies toward Hashimoto bind to the TSH receptor while, rather than promoting TSH action, block the growth of TSH action during illness and have seen positive results throughout the thyroid condition of Graves' Disease [12].

2. Clinical features of Graves' Disease condition

Symptoms of hyperthyroidism associated with thyrotoxicosis are nervousness, overactivity, insomnia, palpitations, mental confusion, weight loss and prominent signs of thyrotoxicosis are tachycardia, atrial fibrillation, hyperreflexia systemic hypertension, warm moist skin, hyperactivity, and tremors. The clinical features predominantly observed in GD are orbithopathy, pretibial myxedema, and goiter.

The pathogenesis of ophthalmopathy includes the immune response to a TSH receptor–like protein in orbital connective tissue initiates cytokine formation further promoting production by orbital fibroblasts of hydrophilic glycosaminoglycan, resulting in high osmotic pressure, fluid accumulation, and clinical ophthalmopathy. Eye muscle antigens include the flavoprotein (Fp) subunit of mitochondrial succinate dehydrogenase, G2s and the FOX P1 protein, a winged helix transcription factor, and their respective antibodies are clinically useful markers in the diagnosis of GD. The respective roles of the connective tissue response and eye muscle antibodies involved in the pathogenesis are under investigation.

3. Pathogenesis

Autoimmune thyroid diseases are the most prevalent organ- specific which includes Graves' Disease (GD) and Hashimoto's Thyroiditis (HT). The hyperactivity of the thyroid gland is due to the production of thyroid stimulating antibodies (autoantibodies) and are known to recognize and activate thyroid stimulating hormone receptor. The autoantibodies produced by TSHR increase the growth and functioning to thyroid follicular cells resulting over production of T3 and T4. It has been suggested by the studies that a genetic clonal lack of suppressor T cells may be responsible for the inappropriate and unregulated production of TSH receptor antibody [13].

3.1 Autoimmunity mechanism

The pathological process involved in Graves' Disease is similar to other autoimmune disease but a unique aspect found in the majority of patients is TSHR antibodies which cannot be found in normal individuals. The characterization of the autoimmunity process includes a lymphocytic infiltrate seen at the target organ and the presence of antigen-reactive T and B cells against thyroid antigens. As in all autoimmune diseases it is observed when self-tolerance is broken; T cells identify self-antigens, and B cells produce antibodies targeting host cells. Many cell

self-specific T cells escape thymic deletion; however, additional mechanisms like clonal anergy and peripheral suppression normally prevent reactions to auto antigen. B cells which recognize a specific cell auto antigen in the lymphoid organs are taken into T lymphocyte areas; B lymphocytes normally kill by apoptosis if they are not activated by T available cells while B lymphocytes, binding soluble self-antigen, are anergised; they down- regulate expression of membrane IgM and live for a short period. B cells are inactivated by T-cells available for support. An additional B cell tolerance mechanism includes allelic exclusion and clonal ignorance in receptor and autoreactive B cell receptor (BCRs).

3.2 The thyroid antigens

3.2.1 Tg and TPO

Thyroglobulin (Tg) is 660 kDa, a dimeric glycoprotein secreted by the follicular cells of the thyroid gland and acts as a substrate for the synthesis of T3 and T4. Besides, it stores an inactive form of thyroid hormone and iodine in the lumen of the thyroid follicle. The antibodies produced in response to Tg induce massive destruction of the thyroid gland but few studies propose to show high levels of Tg do not *perse* induce antibody production. Thyroid hormones are synthesized on the Tg with the help of thyroid peroxidase (TPO). TPO is an enzyme Anti-thyroglobulin antibody (ATA) and TPO- specific T cells are often found in GD patients. Tg antibodies recognize the confirmation of a large fragment of Tg [14]. These are directed against the same epitopes which are mainly observed in GD. Antibodies against TPO are involved in complement/antibody-mediated cell toxicity and target toward conformational epitopes.

3.2.2 GD auto antigen and TSH receptor antibodies

The auto antigen which is mainly expressed in Graves' Disease is thyroid stimulating hormone receptor (TSHR). It is a G protein coupled receptor with 7 trans membrane spanning domains expressed in thyroid gland but also in adipose cells, fibroblasts, bone cells including heart cells [15]. Binding to circulating TSH, a G-Protein signal activates adenylcyclase cascade events and intracellular levels of c AMP increases. Rise in c AMP activates all the functional activities of thyroid cell which includes iodine pumping; synthesis of thyroglobulin, iodination, endocytosis, and proteolysis; activity involving thyroid peroxidases; and hormone release. Literatures suggest that there may be a shedding of the TSHR ectodomain [16–18] even though it has not been confirmed in vivo.

The presence of TSHR-Antibodies (TSHR-Abs) [19] is the most unusual feature of most GD-patients. The early analysis of TSHR-Abs [20] represents the most accurate definition of their features, which resulted by analysis of monoclonal antibodies to the TSHR from various sources, including human, mouse and hamster: mouse and hamster antibodies are secondary to TSHR [21–23]. Three types of TSHR-Ab are identified among autoimmune-thyroid patients and similar diseases are observed in immunized rodents; stimulating, blocking, and so-called "neutral." TSHR-Abs that has proved to be beyond neutral in their biological activity has been characteristic of the TSHR ectodomain's cleavage. Stimulating Antibodies (Stimulating Abs) induce cAMP production and inhibit any simultaneous activation of the thyroid function that bind to naturally conformed TSHR. TSHR blocking antibodies, its main bioactivity of this is to prevent TSH receptor binding in a manner that may cause thyroid problems, and also it act as weak TSH agonists. Such blocking antibodies depend on conformation, and others are very similar to the

decreased TSHR antigen and/or linear peptides. At the end, neutral TSHR antibodies may not prevent or stimulate cAMP production or TSH adhering. Neutral TSHR-antibodies bind only to linear epitopes and are targeted against the "unique region" located in receptor among specific amino acids 316–366 [24]. In GD patients, the presence of different ratios with high-affinity TSHR-Abs contributes to the clinical phenotype. Therefore, a function-based classification of these antibodies appears more relevant than their ability or failure to influence the binding of TSHs or cAMPs.

3.3 Different epitopes of TSHR Abs

3.3.1 Monoclonal antibodies against TSHR

Any monoclonal antibody raised to TSHR protein or antigen includes synthesized peptides and recombinant ones, that have been shown to be neutralizing in mechanism. Only natural intact TSH receptors or genetic immune are used to stimulate thyroid-stimulating antibodies and establish an animal hyperthyroidism model [25–28]. Monoclonal antibodies, such as MS-1, have been raised in hamsters utilizing rare B cells that secrete TSHR-enhancing antibodies [29]. Rodents and humans have been used to identify blocking and neutral monoclonal antibodies (mAbs).

3.3.2 Stimulating TSHR-Ab epitopes

Part of the TSHR ectodomain has also been crystallized with the support of appropriate stimulating monoclonal fragment TSHR Fab bound in situ [30]. Many amino acids have a large section of the concave surface of the TSHR ectodomain that has been identified as important for antibody binding, in the leucin-rich repeat region (LRR). Reviewing recent studies particularly at conformational epitopes using mass spectrometry [29] have shown that epitopes exist outside the LRR for blocking and stimulating monoclonal antibodies. The prominent region exist at N terminal region of the extracellular domain (ECD) has been well demonstrated and also at the residues in the "hinge" region [31].

3.3.3 Blocking TSHR-Ab epitopes

TSHR antibodies block epitopes are widely distributed compared to stimulating antibodies. Thus, blocking TSHR monoclonal antibodies (TSHR-mAbs) have been shown to have binding affinities to independent or confirmational epitopes [32]. In patients with GD or HT, TSHR autoantibodies showed themselves to compete in N-terminal TSHR beta subunit (aa382–415), with a blocking TSHR-mAb. Blocking hypothyroid antibodies therefore is heterogeneous in nature and this repertoire of anti-bodies involves multiple epitopes. Crystallization and modeling of human and mouse blocking TSHR Abs attempting to block and these TSHR-Abs strongly proposed that the N-terminal and the leucine-rich binding are linked [33, 34].

3.3.4 Cleavage TSHR-Ab epitopes

Peptide binding (ELISA) and the monoclonal competition of antibodies in patients with Graves' Disease is shown throughout cleavage (aaa 316–366) (competitive inhibition assay by FACS). The tissues of the TSHR are strongly related. The main linear epitopes in animal GD models are known in the area of cleavage [35].

Such antibodies are not competitive to TSH-borne binding in the cleaved area and are therefore often called "neutral."

3.4 TSHR-mAb induced signal transduction

Through the stimulation of agonist, TSH and TSHR-Abs the TSH receptor seems to be active and enhanced. Intracellular signal transmissions spread through classical GPCR effector proteins with the Gαq and Gαs interaction with the recipient directly.

Docking Gαs into the activated receptor results in an increased adenylatecyclasis activity generated by the cAMP, direct activation of protein kinase A (PKA) and cAMP element-binding protein (CREB). Gαq docking involves PI3 and DAG formation and further activation of Ca2+ and protein kinase C (PKC). Enables Erk1/2 and p90RSK subsequently. Stimulating TSH-mAb has shown to act in a dose-dependent and time-dependent manner via the Gαq-PKC-Akt cascade, and the rat thyroid model (FrTL-5) was found to be relevant on PKA signaling [36, 37]. Monoclonal antibodies, which are frequently detected by point-of-care tests, were also demonstrated to activate non classical TSH receptor pathways, though this was reported as only a few of the studies have shown this. Certain neutral antibodies are not found to increase cAMP, but could signal by means of Akt, c-Raf/ERK1/2/p90RSK, PKC, and PKA/CREB [37].

3.5 Apoptosis in GD

Apoptosis is absolutely essential for the development of the aggressive immune system. The initial theories about thyroidectomy-induced autoimmunity postulated that antibody and T cell-mediated destruction of the thyroid contributed to the death of thyrocytes. In the ensuing years, it is discovered that apoptosis had a part in GD [38]. Apoptosis provided a new insight into autoimmune target destruction, further implying the participation in possible pathogenesis of thyroid autoimmunity from death-controlled receptors and cytokine-related apoptotic pathways. An abnormally increased level of CD4(+) regulatory T cells break host immune tolerance and initiate T-reg apoptosis [39] and, in this way, foster abnormal T-mediated immune activation in patients with GD. Bcl-2 regulatory protein family is recently linked to the pathogenesis of GD [40] looked at apoptotic proteins, and observed a relation to the expression of the Bcl-2 regulatory family in the thyroid follicular cells in GD [41]. Furthermore, the researchers suggested that an increase in apoptotic molecules (Fas/FasL and caspase 8) are present on T and B lymphocytes in GD and HT patients, demonstrating involvement in GD pathogenesis. It is clear to describe in apoptosis, death receptors/ligands play a regulatory role, but caspase-independent mechanisms can also coexist and contribute to GD thyroid cell death.

3.6 Apoptosis and thyrocyte oxidative stress induced by TSHR antibodies

The induction of cell proliferation via stimulating- monoclonal antibodies (mAbs) shown in thyrocyte stimulation studies with TSHR-mAbs that have been conducted with cAMP. Some neutral monoclonal antibodies (mAbs) have been identified as stimulating multiple stress signals and apoptosis induced. These antibodies are responsible for activation of multiple oncogenes, including p53, p73 and Reactive oxygen species (ROS). In addition, endoplasmic reticulum stress protein (gp98) is induced and the expression of heat shock proteins (p27 and p107), hemaoxygenase (HO) and superoxide dismutase (SOD) is further activated and supported.These data support stress signals in the thyroid cells of Graves' Disease.

A morphologic staining (annexin V and propidium iodide) and a quantitative flow cytometry test [42] confirmed the cell death caused by apoptosis, and is likely to confirm the previously described histological evidence that thyroid tissue apoptosis is found in GD patients. These observations have revealed that stress signaling cascades have been involved although oxidative stress alone or cell-specific signaling molecules induced such apoptosis remain unclear. These results also indicated the ability of neutral TSHR monoclonal antibodies (TSHR-mAbs), which is known to activate inborn and bystander immune reactivity via DNA release from apoptotic cells [43], to aggravate the local infiltration in a thyroid. This same phenomenon may be associated with Graves' orbitopathy as these cells were abundantly expressed by activation-induced fibroblast death.

3.7 Humoral immunity

The GD Rodents have shown humoral immunity against other TSHR-immunized antigens, unless outbred animals like hamsters have been used, to show intrathyroid infiltrate. This implies that GD is an intricate genetic disorder, usually associated with autoimmune thyroiditis. AITD is not known for the presence of pendrin antibodies, sodium iodides symporters [44, 45], thyroxine, triiodothyronin [46], tubulin, megalin, calmo-modulin and DNA, or DNA-related proteins [47–49]. The IGF-1 receptor is widespread in B cells and in fibroblast from GD patients, although over-expressed. In activation of the thyrocyte, synergism between antibodies to TSHR and the IGF-1 receptor was suggested. That requires further research as TSH and IGF-1 or insulin are commonly known to induce proliferation of thyroid cells.

4. Diagnosis

Diagnosis of GD is complex and difficult. The combined effect of several symptoms and symptoms leads the doctor to suspect the thyroid irregularity. Comprehensive history such as intake or exposure to iodine, drugs, thyroid and autoimmune history and physical exam, vital signs such as pulse rate measurement, blood pressure measurement, respiratory and body weight. Moreover, the presence or absence of a thyroid tenderness, symmetry and nodularity should also be evaluated; pulmonary, cardiac and neuromuscular function and the presence of eye signs or pretibial myxedema. Because hyperthyroidism is frequently associated with low or undetectable levels of TSH, it is an easy biochemical diagnosis to make if thyrotoxicosis is found. T4 and T3 are usually high, but are relatively higher in GD serumT3 than T4. The T4 and T3 concentration levels are usually high. In mild forms of hyperthyroidism and during earliest phases of DG only serum T3 levels can be enhanced (T3 toxicosis). The removal of the lid, anxiety, an increase in neck volume, signs of involvement with the eye and the history of autoimmune disease in the family also distinguish GD from other types of hyperthyroidism (e.g., toxin goiter, toxic adenoma) (e.g., silent or subacute thyroiditis, exogenous thyroid hormone use). Serum measurement of the TSH-receptor automatic antibody (TRAb) helps confirm diagnosis. New bioassays for the thyroid stimulant immunoglobulin (TSI) especially aid in the measurement of TSI's ability to increase the intracellular cAMP level by detecting stimulating antibodies. Radioactive Iodine uptaking (RAIU), despite a clinical examination, thyroid function evaluation and TRAb detection should only be carried out when the diagnosis is unclear. The pattern for iodine uptake in GD is diffuse if no coexisting nodules or fibrosis do not occur. Technetium

99 can be of assistance. Increased color Doppler flow supports thyroid hyperactivity diagnosis. In case of thyroid nodularity in the neck or in a thyroid scintigram, thyroid scan must be conducted.

5. The factors that influence the recurrence in GD patients

5.1 Biochemical parameter

The severity is linked to recurrence risk in ATD-treated GD patients. Partly the biochemical parameters help to determine the seriousness of GD. The parametric increase of serum T3, which is affected by increased intrathyroid type 1 deiodinase activity, is significant in untreated GD. Independent GD factors influenced free thyroxine-to-free triiodothyronine ratio (FT3 andFT4) is predictive for the ATD treatment outcome for patients with GD. Hyperthyroidism symptoms observed after the treatment with beta-blockers. Patients with a higher T3/FT3 or FT3/T4 serum ratio have been found to be more at recurrence, requiring a longer and more additional dose in the treatment. The risk of relapsed treatment is increased for patients with a higher serum T3 and FT3/FT4 ratio. When a patient has a high T3/T4 ratio, therapy should be continued for at least one year after the ATD has been removed. Serum thyroid-stimulating hormone (TSH) should be measured. However, as it is known, the thyroid hormone has a negative feed-back influence on the TSH. Thus, prior research has established that drug discontinuation is associated with elevated levels of TSH. These findings suggest that treatment with a prolonged ATD may be indicated for GD patients who do not normalize their thyroid-stimulating hormone levels quickly.

5.2 Immune parameters

The GD is the result of hyper-activation by TRAb of the TSH receptor in follicular thyroid cells. In approximately 95% of newly diagnosed GD patients, TRAb is positive and higher TRAb levels are indicative of serious immune disorder. Recent times have demonstrated TRAb as a helpful and qualitative prognostic indicator for ATD therapy. At the time of GD diagnosis, patients with high TRAb levels had a considerably higher recurrence risk, while TRAb patients were often more likely to get long-term recovery. Switching from positive to negative TRAb in GD patients involves a reduced immune disorder after ATD therapy. In the prognosis of GD patients, TRAb levels were also observed at ATD withdrawal. Recurrence risk was noted to be increased in TRAb-positive GD during the time of drug discontinuation. New assays can be used to distinguish the stimulating (stimulating) and blocking (disturbing) effects of medications on antigen responses. Thyroid stimulating antibodies (TSAb) antibodies are found to be predominant in GD patients. Recently, the value of TRAb for patients on GD treatments for recurrence risk with prediction has been shown to be greater than that of GD, particularly TSAb. GD patients with thyroiditis from Hashimoto appear to be remission after Hashimoto's thyroiditis due to advanced harm. The prevalence of peroxidase/peroxidase antibodies is highest in people with Hashimoto's thyroiditis. Few studies have analyzed whether the existence of Thyroid peroxidase antibodies (TPOAb) and Thyroglobulin antibodies (TgAb) autoantibodies is linked to the risk of a subsequent relapse in those with GD. People with GD may also show low TPOAb and TgAb levels, and in such cases, the clinical and laboratory findings are not completely consistent with the diagnosis of Hashimoto's disease.

5.3 Goiter size

A major clinical manifestation found in GD patients is the large goiter. Previous studies show a large predictor of increased risk of recurrence in GD patients after the removal of ATD, goiter size. Findings from 5 years of trail follow-up have shown that the rate of remission for normal or mild-goiter patients is higher than for large-goiter patients. GD patients with significantly lower goiter sizes tend to have higher rates of remission after ATD treatment. Enlarged goiter size at the time of GD diagnosis and drug withdrawal is associated with a higher recurrence risk of GD.

5.4 Graves' orbitopathy

At the time of diagnosis of GD, Graves' orbitopathy is observed in 35% of patients. Sometimes, the presence of the Graves orbitopathy indicated that the immune system gets worsen. Previous studies show that the risk of GD recurrence after withdrawal of ATD in patients with Graves' orbitopathy is higher [38]. An Eckstein et al. study even found that GD patients with severe Graves' orbitopathy only received a 7% remission rate. Although the recurrence rate is higher, the ATD treatment remains a preferred therapeutic option for GD patients with orbitopathy of Graves because Graves's orbitopathy improves as well as a steady eutyroid status achieved and reduces inflammatory markers of the TRAb. Recent studies have demonstrated that the continuous low dose of ATD has helped to improve GD disease in Graves orbitopathy patients.

5.5 Genetic factors

Genetic factors plays a key role in the pathogenesis of GD and increase the risk of recurrence to the development of GD. Several studies supports both cytotoxic T-lymphocyte-associated factor 4 (CTLA4) rs231775 and rs231779 polymorphisms were strongly associated with recurrence of GD even after ATD withdrawal in Asians, while there is no association in Caucasians for developing GD. In Caucasian patients with GD, the recurrence risk after ATD withdrawal was observed with the polymorphisms of HLA DQA2, HLA DRB1∗03, and HLA DQB1∗02. The HLA region majorly contains immune response genes and tHLA polymorphisms might also influence the outcome of GD patients by regulating the immune system.

5.6 Environmental factors

GD starts with some environmental factors in the predisposed genetic association in individuals. Stress is one of the important environmental considerations, and a majority of the studies have supported the association between stress and recurrence in GD patients after ATD therapy. The overall stress score for large life events was significantly higher in the recurrence group in a prospective study that examined the recurrence risk of GD in patients than in the remission. Another trial showed that the recurrence group was more stressful than the remission patients, and that the total number of stressful events is linked to the number of the recurrence. Psychosocial stress is an important part of a stressful event. It is worth mentioning. Previous trials showed that the risk of GD recurrence is higher than that of GD patients without such a disease for patients with psychiatric disorders as depression and hypochondriasis. Therefore, reducing stress is an essential way of improving the prognosis of ATD-treated GD patients. Another ecological factor is iodine intake.

The synthesis of the thyroid hormone is based on Iodine. Increased content of iodine in thyrocytes has promoted degradation of ATD and reduced uptake of ATD. The supplementation of iodine increased the GD recurrence rate. After ATD withdrawal hyperthyroidism in euthyroid GD patients arose when pharmaceutical doses of iodine were taken. Epidemiologic studies have shown, however, that in iodine-adequate countries, recurrence rates in GD patients do not exceed those in iodine-deficient areas following ATD withdrawal.

6. Conclusion

Autoimmunity is a collection of heterogeneous disorders which is controlled by complex genetic and environmental factors. In GD, the prominent antigen responsible is TSHR and the studies of extra thyroidal TSHR expression in different variety of cell types and immune cells has added to the complexity of the disease and also introduced a variety of potential new mechanisms that may be involved. A common approach of GD is that TSHR-Abs promote the disease by enhancing thyroid antigen expression. Precision medicine's promise is still important in the future. The chapter has personalized diagnostic and therapeutic approaches will encompass both a patient's genomic makeup and their environmental factors.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

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