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Recent Advances in Autoimmune Thyroid Diseases

Won Sang Yoo, Hyun Kyung Chung

Division of Endocrinology and Metabolism, Department of Internal Medicine, Dankook University College of Medicine, Cheonan, Korea

Autoimmune thyroid disease (AITD) includes hyperthyroid Graves disease, hypothyroid autoimmune thyroiditis, and subtle subclinical thyroid dysfunctions. AITD is caused by interactions between genetic and environmental predisposing factors and results in autoimmune deterioration. Data on polymorphisms in the AITD susceptibility genes, related environmental factors, and dysregulation of autoimmune processes have accumulated over time. Over the last decade, there has been progress in the clinical field of AITD with respect to the available diagnostic and therapeutic methods as well as clinical consensus. The updated clinical guidelines allow practitioners to identify the most reasonable and current approaches for proper management. In this review, we focus on recent advances in understanding the genetic and environmental pathogenic mechanisms underlying AITD and introduce the updated set of clinical guidelines for AITD management. We also discuss other aspects of the disease such as management of subclinical thyroid dysfunction, use of levothyroxine plus levotriiodothyronine in the treatment of autoimmune hypothyroidism, risk assessment of long-standing antithyroid drug therapy in recurrent Graves' hyperthyroidism, and future research needs.

Keywords: Autoimmune thyroid disease; Graves disease; Hashimoto disease

INTRODUCTION

Autoimmune thyroid disease (AITD) is a prototypical organ-specific autoimmune disease. The etiology of AITD is multifactorial; interactions between genetic and environmental predisposing triggers lead to dysregulation of immune tolerance. The incidence of the two main clinical presentations of AITD, Graves disease (GD) and Hashimoto's thyroiditis (HT), is estimated at 5% of the population [1]. Despite developments in effective diagnostic and therapeutic methods, there are outstanding issues in the treatment of AITD such as difficulties in treatment decision for patients with subtle changes in thyroid function and limitations in the definite treatment of hyperthyroidism without destroying or removing the thyroid gland. Therefore, it is essential to understand the etiological background of AITD and evaluate the existing clinical data to better determine the ideal management method. In this review, we focus on recent advances in understanding AITD and the controversial clinical issues.

PATHOGENIC MECHANISMS OF AUTOIMMUNE THYROID DISEASE

It has been known that there are polymorphisms in the AITD-related genes for quite some time. Among these genes, polymorphisms in the thyroid-stimulating hormone receptor (TSHR) gene contribute to susceptibility to GD [2]. Recently, a specific single-nucleotide polymorphism (SNP) in the TSHR gene relat-

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Corresponding author: Hyun Kyung Chung
Department of Internal Medicine, Dankook University College of Medicine, 119 Dandae-ro, Dongnam-gu, Cheonan 31116, Korea
Tel: +82-41-550-3057, **Fax:** +82-41-556-3256,
E-mail: chkendo@dankook.ac.kr

ed to central tolerance has been identified. Homozygosity or heterozygosity for the receptor SNP rs179247 displayed significantly decreased intrathymic expression of TSHR mRNA transcripts, which could underlie the decreased central tolerance and increased risk of GD [3]. In central tolerance, identification of the autoimmune regulator (AIRE) gene as the susceptible locus for autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED) provided a new window to understand the maintenance of self-tolerance [4]. AIRE is a transcription factor regulating the expression of many proteins in medullary thymic cells; defects in the AIRE gene lead to dysregulation of central immune tolerance and multi-organ autoimmune defects. Although mutation in the APECED gene does not directly lead to AITD susceptibility, APECED patients in certain areas showed a high positive rate of thyroglobulin antibodies and a novel AIRE mutation (G228W) closely cosegregated with autoimmune thyroiditis in a family with APECED [5].

Genes regulating the immune response carry the key for the progression of AITD. Along with major histocompatibility complex (MHC) class I and II genes, cytotoxic T lymphocyte-associated factor 4 (CTLA4), CD40, CD25 (FoxP3), protein tyrosine phosphatase, non-receptor type 22 (PTPN22), and the cytokine regulatory genes have been identified as the major players in AITD [6]. CTLA4 was the first non-human leukocyte antigen (HLA) gene to be associated with GD. A recent meta-analysis of the A49G SNP in CTLA4 found an increased risk of HT in East Asians and GD in the Chinese population [7]. Previous data on PTPN22 showed contradictory results, although a meta-analysis of the C1858T polymorphism revealed an association with GD [8]. CD40 is the immune regulatory gene of the tumor necrosis factor (TNF) superfamily and is expressed on thyroid follicular cells; CD40 C/T1 polymorphism is known to correlate with GD [9]. A recent large-scale study found an association with an interleukin 1 (IL-1) receptor antagonist variable number of tandem repeats IL-1 receptor antagonist gene (IL-1 RN) variable number of tandem repeats (VNTR) polymorphism in 202 HT patients [10], and another study found an association between the rs763780 polymorphism in IL17F and HT in Chinese patients [11]. The SNP in the signal transducer and activator of transcription (STAT) family protein, which is the transcription factor regulating immune-regulatory pathways and cytokine signaling, has been found to be associated with HT as well as GD [12].

Although not specific to the thyroid, selenoprotein (SEP) is involved in the deiodination of the thyroid hormone; a recent study found a significant association with a SNP in the promoter of SEP S gene (SEPS1) in patients with HT [13]. It is not known if dietary selenium is related to the development of AITD. Previous data showed that inadequate selenium intake might exacerbate HT; however, a recent meta-analysis found that selenium supplementation in HT had no beneficial effect [14]. The ongoing the chronic autoimmune thyroiditis quality of life selenium trial (CATALYST) may further reveal the role of selenium in the pathogenesis of AITD [15]. Although how these genetic factors contribute to immune dysregulation is not yet clear, we expect that this knowledge will be extremely valuable in developing individualized and tailored therapeutic approaches for AITD.

Recent studies on the environmental triggers of AITD have identified selenium and vitamin D to be the chief dietary components. A low vitamin D level is not only an etiological factor, but is also related to the severity of AITD. A recent meta-analysis showed that patients with GD were more likely to have vitamin D deficiency [16]. However, whether vitamin D supplementation exerts any beneficial effects on the onset and pathogenesis of GD has not been determined, although the role of vitamin D in AITD is still being investigated [17]. There is strong evidence that several anticancer drugs (cytokines, interferon α, and tyrosine kinase inhibitors) can induce thyroid dysfunction [18]. After years of debate, moderate consumption of alcohol has been proven to be protective in AITD, although the exact mechanism remains unclear [18]; the role of smoking is still being investigated. Rapid industrialization and exposure to environmental toxins are also considered as causative factors of AITD. One study found an increased HT incidence among individuals residing near petrochemical complexes [19]. Climate also affects autoimmunity; women living in Siberia showed a high prevalence of thyroid peroxidase (TPO) antibodies [20]. Thus, global warming and rapid changes in the weather might contribute to the increased incidence of autoimmune diseases.

Based on genetic predisposing factors and environmental triggers, dysregulation of the immune system results in an immune attack on the thyroid. A typical finding in AITD is intrathyroidal infiltration of T and B lymphocytes which have a critical role in the pathogenesis of AITD. In cellular immunity, relatively newly identified regulatory T cells (Tregs) and follicular helper T (Tfh) cells have come into the spotlight for their roles in the pathogenic mechanism of AITD. Tregs represent 5% to 10% of CD4+ cells and express immune responses by direct cell-to-cell interaction or indirectly through cytokines such as transforming growth factor β (TGF-β) and IL-10. Altered Treg activity has been observed in patients with AITD [21]. Tfh cells exert pro-

moter function in antigen-specific B cells through IL-21 production. Increased amounts of Tfh cells in peripheral blood have been found to correlate with thyroid-specific antibody levels in HT patients [22]. Defects in Tregs and activation of Tfh cells are generally accepted as the initiating events in AITD. In the case of cytokines, a subset of Th3, which chiefly synthesizes TGF-β, and Th17 cytokines including IL-17 and IL-22 have been identified as additional players in AITD. These cytokines have a role in the chronic inflammatory condition, particularly in HT [23]. It has been suggested that IL-22 has a role in antibody production since IL-22 levels correlate with TPO antibody levels in HT [24].

CLINICAL UPDATES IN AUTOIMMUNE HYPOTHYROIDISM

Since Hakaru Hashimoto first described AITD in 1912, significant progress has been made in our understanding of this chronic autoimmune inflammatory condition in the thyroid. Recently, "immunoglobulin G4 (IgG4) thyroiditis" has been added as a unique subtype of HT [25]. Histologically and clinically, it is characterized by fibrosis, lymphoplasmacytic infiltration, degeneration of follicular cells, rapid progression of hypothyroidism, more diffuse low echogenicity, higher antibody levels compared to non-IgG4 thyroiditis, and a lower female-to-male ratio. Although definite diagnostic criteria are not yet available, >20 IgG4-positive plasma cells per high-power field and >30% IgG4-positive/IgG-positive plasma cells have been proposed as diagnostic criteria for IgG4 thyroiditis [25]. Whether the fibrous variant of HT and Riedel's thyroiditis fall within the spectrum of systemic IgG4 diseases is still being investigated [26].

Although we have several up-to-date management guidelines for "subclinical" hypothyroidism [27], treatment decision-making is a relatively vague aspect. To begin with, the fundamental concept of "subclinical" has been questioned. Considering the progressive changes in the levels of serum TSH and free thyroxine (T4), it might be better to develop a "grading" system rather than differentiating between the "clinical" and "subclinical" forms [28]. It is not easy to determine the ideal starting point for thyroid hormone supplementation. Not all subclinical hypothyroid subjects with similar levels of TSH and free T4 develop symptoms. The majority of epidemiological and clinical data shows that thyroid hormone therapy has benefits in cardiovascular conditions, chiefly in the middle-aged group, but not in the elderly [29]. Thus, the normal range of TSH depends on patient age. Individuals may also have a narrow "normal" TSH reference range [30]; in fact, recent studies have found a risk of adverse health outcomes even within the reference range [31]. That is, the upper and lower limits of the normal TSH reference range can be marked as "unsafe" zones. Furthermore, none of the ongoing long-term randomized clinical trials are equipped to explain the benefits of treatment. Therefore, it is necessary to study the physiological and pathological mechanisms underlying functional changes in the thyroid, and there is an urgent need for the accumulation of extensive prospective clinical data on subtle thyroid dysfunction. Fortunately, the European Commission has recently initiated the thyroid hormone replacement for subclinical hypothyroidism trial (TRUST), a multicenter, double-blind, placebo-controlled, and randomized trial with 3,000 adults (≥65 years old) [32]. This trial will definitely aid in understanding the effects of levothyroxine (LT4) treatment in subclinical hypothyroidism.

Approximately 5% to 10% of hypothyroid patients complain about persistent symptoms, despite receiving LT4 treatment and having normal serum TSH levels [33]. Possible explanations of this finding include differences in individual sensitivity, combined autoimmune diseases or AITD on its own, and the inability of LT4 treatment to restore T4 and triiodothyronine (T3) concentrations to physiological levels in the serum and tissue. Recently, the European Thyroid Association (ETA) has provided a guideline for the use of LT4+levotriiodothyronine (LT3) combination therapy in hypothyroidism [34]. This guideline states that there is insufficient evidence that LT4+LT3 combination therapy is superior to T4 monotherapy, and that LT4 monotherapy should remain the standard method of treatment for hypothyroidism. LT4+LT3 combination therapy can be attempted on an experimental basis (13:1 and 20:1 dose ratio by weight) in patients with persistent complaints even with normal TSH levels. The mechanisms underlying psychological well-being and preference for LT4+LT3 combination therapy might be related to polymorphisms in thyroid hormone transporters and deiodinase [34]. Further studies on the variations in the deiodinase gene, development of other iodothyronines or their metabolites such as thyronamines [35], and graded, individualized management of hypothyroidism are warranted.

CLINICAL UPDATES IN AUTOIMMUNE HYPERTHYROIDISM

GD is traditionally treated by three methods: antithyroid drugs, radioactive iodine, and surgery, which have been used continuously since the mid-1900s. A century later, an up-to-date con-

sensus and guidelines for the management of GD based on clinical experience and past studies have been provided by the American Thyroid Association [36], Korean Thyroid Association [37], and ETA as a survey of clinical practice patterns [38]. These guidelines indicate persistent and definite differences in the management of GD worldwide which can be attributed to the clinical decision-making attitude, individual preferences, and medical insurance system in each country. Although these recommendations help survey current practices and identify optimal methods for patient care, they still do not cover every clinical setting. For example, the existing guidelines do not have specific recommendations for atypical cases or dealing with refractory or serious side effects of antithyroid drugs. Several recent case reports presented suggested paths for the management of such rare and atypical cases. A Korean patient who was refractory to antithyroid drug treatment was successfully managed with cholestyramine [39], and serious hepatic dysfunction caused by the antithyroid drug was managed with hemodialysis [40]. The utility of potassium iodide [41] and lithium carbonate [42] as an adjuvant therapy has also been examined. Presentation of these difficult cases is vital when attempting to fill the gaps and cracks in existing knowledge and guidelines.

Subtle hyperfunctioning of the thyroid is also a controversial area. Pre-existing guidelines only provide an outline for the clinical management of patients with subclinical hyperthyroidism. Fortunately, a recent detailed guideline for subclinical hyperthyroidism has been provided separately [43]. According to this guideline, identification of endogenous thyroid disease as an etiological factor should be the first step in the management of subclinical hyperthyroidism, followed by grading based on the severity of thyroid dysfunction. Evaluation of combined risk factors (e.g., atrial fibrillation, cardiac dysfunction, and osteoporosis) is another important part of management. Although these guidelines are not supported by randomized controlled trials, data from several recent meta-analyses provide evidence that treating subclinical hyperthyroidism in patients with undetectable TSH levels can help manage the additional risks of total mortality, cardiac dysfunction, incident atrial fibrillation, and fractures [44,45]. Further research in this field should focus on the etiological basis of this mild change in thyroid function to determine if it is related to a mild form of GD, a certain stage of chronic autoimmune thyroiditis, or other types of endogenous autoimmune thyroid dysfunction. Large-scale, prospective, long-term clinical studies to evaluate the efficacy of treatment are also necessary.

Compared to other regions, Asian countries tend to choose long-term antithyroid drug treatment over radioiodine therapy, not only for first-line therapy but also in recurrent cases [36, 37]. In fact, the reported overall remission rates of long-term, low-dose maintenance therapy with antithyroid drugs are fairly acceptable [46]. However, some GD patients do not attain complete remission with antithyroid drug treatment even after long-term therapy. Therefore, clinicians are interested in discriminating between groups with favorable and unfavorable responses to antithyroid drugs. History of GD, larger goiter size, and presence of TSH-stimulating antibody at the time of drug withdrawal are well-known unfavorable factors [47]. Several recent studies have identified additional correlating factors such as the course of the drug withdrawal program (slow tapering is more favorable than an abrupt end) [48], duration of low-dose maintenance therapy [46], and redevelopment of TSH-stimulating antibody during low-dose maintenance therapy [49]. Intrinsic genetic factors such as PTPN22 C/T polymorphism and the HLA subtypes DQB*01, DQA1*05, and DRB1*03 have been identified as predictors for recurrence; researchers have attempted to develop a prediction model based on the combination of clinical factors and intrinsic genetic markers [50]. In the wave of "precision medicine," evaluation of individual patients based on their genetic background could be a useful approach to develop personalized management programs [51].

Each therapeutic method of GD has its own advantages and disadvantages, but none of them constitutes a definite treatment method because they cannot completely correct the pathogenic autoimmune process. To overcome this hurdle, recent studies have focused on additional therapeutic options to permanently treat hyperthyroidism without destroying or removing the thyroid gland. The chief strategy is to develop an inhibitory factor against the stimulating antibody of the TSHR. Development of biological agents with immunomodulatory activity, such as anti-TSHR antibodies, could lead to a new drug treatment for autoimmune hyperthyroidism [52]. Small molecule inhibitors of TSHR binding and/or activation have been presented as "selective TSH receptor antagonists" [53]. *In vitro* data using model cell systems and primary cultures of human thyrocytes showed effective inhibitory functions of these selective TSHR antagonists [54]; in fact, the results of recent *in vivo* experiments are quite promising [55]. Although there are many limitations such as cost, adverse effects, and lack of remission after discontinuation of these drugs, it is clear that this new drug has the potential to open a completely new domain in the treatment of GD.

CONCLUSIONS

From subtle changes to life-threatening deteriorations, AITD contains broad spectrum thyroid dysfunctions. Recent studies have mainly focused on the consensus for general guidelines of various AITD, and also on the understanding of ideal approaches for each specific condition of AITD. Subgroup identification of Hashimoto's disease, reconsideration of long-term low dose antithyroid drug therapy in patients with Graves disease and LT4+LT3 combination therapy in hypothyroid patients are the issues with ongoing discussions. Further studies of pathophysiologic mechanisms along with genetic backgrounds of AITD will help to develop the definite and individualized therapeutic methods of AITD.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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