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Association of autoimmune thyroid disease with type 1 diabetes mellitus and its ultrasonic diagnosis and management

AITD and T1MD: A common comorbidity

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Abstract

As a common hyperglycemic disease, type 1 diabetes mellitus (T1DM) is a complicated disorder that requires a lifelong insulin supply due to the immune-mediated destruction of pancreatic β cells. Although it is an organ-specific autoimmune disorder, T1DM is often associated with multiple other autoimmune disorders. The most prevalent concomitant autoimmune disorder occurring in T1DM is autoimmune thyroid disease (AITD), which mainly exhibits two extremes of phenotypes: hyperthyroidism (Graves' disease, GD) and hypothyroidism (Hashimoto's thyroiditis, HT). However, the presence of comorbid AITD may negatively affect metabolic management in T1DM patients and thereby may increase the risk for potential diabetes-related complications. Thus, routine screening of thyroid function has been recommended when T1DM is diagnosed. Here, first, we summarize current knowledge regarding the etiology and pathogenesis mechanisms of both diseases. Subsequently, an updated review of the association between T1DM and AITD is offered. Finally, we provide a relatively detailed review focusing on the application of thyroid ultrasonography in diagnosing and managing HT and GD, suggesting its critical role in the timely and accurate diagnosis of AITD in T1DM.

Key Words: Type 1 diabetes mellitus; Autoimmunity; Autoimmune thyroid disease; Ultrasonography; Diagnosis

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Core Tip: Although type 1 diabetes mellitus (T1DM) is an organ-specific autoimmune disease, patients with this disease are more prone to develop other autoimmune disorder, and the most prevalent autoimmune disorder in T1DM patients is autoimmune thyroid disease (AITD). Undiagnosed and untreated AITD may lead to metabolic disturbances and impair diabetes care in T1DM patients, warranting regular and long-term observation. We herein offer an updated review of the basic characteristics of both diseases and factors contribute to their concomitant presence. Additionally, we focus on the role of thyroid ultrasonography in the diagnosis and management of AITD.

INTRODUCTION

INTRODUCTION

As a common childhood-onset chronic disorder, type 1 diabetes mellitus (T1DM) affects 1:300 children, and the disease incidence has continued to increase in recent decades[1, 2]. The incidence of T1DM is not uniform across the world, and it tends to be higher in higher-income countries than in lower-income countries[3]. As a result of the autoimmune attack predominantly driven by T cells, T1DM occurs in genetically predisposed individuals exposed to environmental and stochastic factors, leading to the dysfunction and death of pancreatic β-cells, with subsequent hyperglycemia[4]. However, although T1DM is an organ-specific autoimmune disorder, individuals with T1DM often exhibit a higher risk of additional autoimmune disorders[5]. The concomitant presentation of T1DM and another autoimmune disorder may complicate

diabetes management and result in varying clinical symptoms, thus seriously influencing patient quality of life[6]. Among these additional autoimmune disorders co-occurring among children and adolescents with T1DM, autoimmune thyroid disease (AITD) accounts for the highest proportion[7]. As the most prevalent organ-specific immune-mediated disorder in the world, AITD is characterized by autoreactive lymphocyte infiltration in the thyroid and the presence of autoantibodies targeting thyroid antigens[8]. Clinically, thyroid dysfunctions, which include hyperthyroidism and hypothyroidism[9], lead to metabolic disturbances and may impair diabetes management in T1DM. Therefore, it is important for individuals with T1DM to regularly screen for thyroid disorders, allowing for the early detection, early diagnosis and intervention of thyroid dysfunction. Benefiting from advances in ultrasound technology, ultrasonography has been widely used to evaluate and treat thyroid diseases[10]. Here, we aim to provide an updated review about the relationship between T1DM and AITD as well as the current status of ultrasonography application in AITD.

THE BASIC CHARACTERISTICS OF T1DM AND AITD

T1DM

As described above, the estimated incidence of T1DM is increasing in many areas around the world. However, these incidences of T1DM may be underestimated. These numbers do not include many adults with T1DM, as almost all incidence data are derived from registered individuals under 20 years of age[11]. Additionally, there is a clear male predominance in T1DM individuals, and this may be associated with the protective role of estrogen[12].

Although the etiology and pathogenesis mechanisms of T1DM have many unknow and large knowledge gaps, our understanding of its pathological process has greatly improved during the last two decades. It has been suggested that a complicated interaction among genetic, environmental, and immunologic factors induces a T-cell-regulated immune attack directed against pancreatic β cells[4, 13]. Genetic studies have revealed that T1DM genetic susceptibility exhibits a polygenic nature. Currently, there are more than 60 gene loci linked to T1DM[4]. Among them, the human leukocyte

antigen (HLA) class II genes involved in antigen presentation exhibit a major risk factor for T1DM, and HLA-DR and HLA-DQ show the strongest relationship with this disease[14]. In addition, various other immune-related loci (non-HLA) connected to T1DM are recognized, such as *CTLA4* (cytotoxic T-lymphocyte antigen 4) and *PTPN22* (protein tyrosine phosphatase non-receptor type 22). Furthermore, various candidate genes as well as noncoding RNAs have been identified based on genome-wide association studies (GWAS)[15]. This strong genetic component of T1DM has stimulated efforts to develop a T1DM genetic risk score (T1DM-GRS) based on single-nucleotide polymorphism (SNP) genotyping, as it would be useful for evaluating and predicting islet autoimmunity progression as well as T1DM development in high-risk individuals[16].

However, compared to genetic factors, environmental influences remain poorly understood despite intensive research. The increasing incidence, twin studies, and immigrant studies indicate that environmental factors also exhibit a major role in contributing to T1DM development[17]. Numerous research findings have indicated that the environmental triggers connected to T1DM mainly include climatic conditions, diet, lifestyle, obesity, toxins, vitamin D sufficiency, and infections[17, 18]. All these factors may lead to gut microbiota dysbiosis and influence the interrelationship between the intestinal microbiota and host immune system, potentially contributing to T1DM[19, 20]. However, some research results related to the role of various environmental factors are largely controversial[21, 22], and this may reflect the heterogeneity of T1DM. Therefore, further work concerning the role of gene-environment interactions in contributing to T1DM development is needed.

Influenced by potential genetic and environmental factors, β cell-directed autoimmunity, which includes humoral and cell-mediated autoimmunity, is triggered during the initiation of the development of T1DM. Before clinical symptoms present, there is a long preclinical stage, characterized by the production of disease-specific autoantibodies and reduced insulin and C-peptide production and secretion. The best-characterized autoantibodies connected to T1DM are those that recognize islet cells,

insulin, glutamic acid decarboxylase 65, islet tyrosine phosphatase 2, and zinc transporter 8[23]. These nonpathogenic autoantibodies can be viewed as biomarkers of the autoimmune process. Therefore, according to the appearance of autoantibody(ies) and clinical manifestations, a disease staging classification system has been introduced to evaluate and predict T1DM progression in genetically at-risk individuals[24]. Three stages have been defined, starting from serological autoimmunity (≥ 2 disease-related autoantibodies with normoglycemia, stage 1) to a second stage of dysglycemia (stage 2), and to definitive diagnosis of T1DM (stage 3). As it is important to guide the predication and prevention of T1DM, this classification scheme should be further revised by identifying novel stage-specific biomarkers[25, 26]. In nonobese diabetic (NOD) mice, both $CD4^+$ and $CD8^+$ T cells contribute to T1DM development, and in individuals with T1DM, T cells targeting T1DM-related autoantigens can be observed in the pancreatic lymph nodes (PLNs) and islets[27, 28]. The participation of these potentially pathogenic T cells in the immune attack toward β-cells suggests the failure of immune system regulation. Of note, the gatekeeper role of regulatory T cells (Tregs) is important to maintain immunological tolerance and prevent autoimmune disease[29]. Thus, a reduction in different Treg populations, especially $CD4^+CD25^+Foxp3^+$ Tregs, contributes to the development of T1DM[30]. As a result, various immune cells infiltrate the islets, resulting in insulitis. Insulitis is an early pathologic hallmark of this autoimmune disorder and eventually causes the death of β-cells and a reduction in insulin[31]. In addition, it has been proposed that β-cells are not merely passive targets of autoimmune reactions but also contribute to the initiation of this complex autoimmune process[32, 33].

At present, there are no widely accepted and validated diagnostic criteria for T1DM. Instead, its clinical diagnosis still mainly depends on two main features, including insulin deficiency as well as the presence of the corresponding autoantibodies. However, additional criteria are needed as the diagnostic accuracy of the above criteria in individuals who develop diabetes over the age of 20 years is less informative[34]. Once diagnosed, individuals with T1DM must rely on exogenous insulin for glycemic control

to avoid ketoacidosis and hyperglycemia-related complications[35]. However, insulin therapy does not represent a cure and often fails to achieve optimal blood sugar management in many patients. Based on the understanding of its heterogeneity and early-stage development as described above, more personalized medicine approaches should be designed to diagnose, prevent, and hopefully treat T1DM[36, 37]. However, as an autoimmune disease, the ultimate optimal goal of T1DM treatment is to restore immune tolerance toward disease-specific autoantigens to avoid autoimmune attack against β-cells. For this purpose, combination therapy based on antigen-specific immunotherapy exhibits promising prospects[38, 39].

AITD

As the most prevalent organ-specific autoimmune disorder all over the world and the most prevalent pathological condition associated with the thyroid gland, AITD affects approximately 5% of the total world population[40]. Graves' disease (GD) and Hashimoto's thyroiditis (HT) represent its two main clinical manifestations. The incidence of HT in females and males is approximately 3.5/1000 and 0.6/1000, respectively, with a global prevalence of 2 to 3%. GD influences 1 to 2% of females and 0.1 to 0.2% of males[40]. In contrast to the male predominance in T1DM, AITD shows a strong female preponderance, which may result from the immune-enhancing activity provided by estrogenic sex steroids[41]. Thus, the reasons behind these sex differences in these autoimmune diseases deserve more attention and research in the future.

As a result of immune imbalance, tolerance toward thyroid-specific autoantigens, such as thyroglobulin (Tg), thyroperoxidase (TPO) as well as thyroid-stimulating hormone receptor (TSHR), lost, leading to an immune destruction of thyroid tissue, yielding AITD[40]. Autoreactive T and B lymphocyte infiltrates within the thyroid and the presence of antibodies targeting the above thyroid self-antigens (anti-Tg, anti-TPO, and anti-TSHR antibodies) can directly confirm that autoimmune reactions occurr in both GD and HT. Compared to those in GD, lymphocyte infiltrates in HT are more severe, and therefore, HT patients exhibit the destruction of thyroid follicles, leading to low thyroid function (hypothyroidism)[42]. However, as the production of TSHR-specific

stimulating antibodies (TSAbs) is redundant in GD, thyrocyte proliferation, thyroid growth, and the production of thyroid hormones are induced, finally inducing hyperthyroidism[43]. Both diseases exhibit different clinical manifestations. However, HT and GD share similar immunogenetic mechanisms, and conversion between conditions can occur[44, 45].

During the last two decades, major progress on the mechanisms underlying the development of AITD has been made based on extensive research. Generally, it is believed that a complicated interaction between genetic susceptibility and environmental risk factors, together with various epigenetic factors, contributes to the pathogenesis of AITD[40, 42, 43]. Among these factors, genetic factors predominate, as they account for 70 to 80% of the risk of developing thyroid autoimmunity based on twin/family studies. Environmental factors account for the remaining 20 to 30%[46, 47]. The identification of genes associated with AITD susceptibility has contributed to a better understanding of disease- causing mechanisms and has indicated that the presence of the related genes exacerbates AITD risk[48]. The main known AITD susceptibility genes can be mechanistically divided into general immune-regulatory genes (such as *HLA-DR3*, *CTLA-4*, and *PTPN22*) as well as thyroid-specific genes, such as the genes encoding the corresponding autoantigens (*Tg*, *TPO*, and *TSHR*). In addition, various novel candidate risk genes for AITD, such as *FCRL3* (FCReceptor-Like-3), *SCGB3A2* (secretoglobin 3A2), and *TNFR 2 (tumor necrosis factor receptor 2)*, have been described by GWAS and immunochip analysis[40, 49]. As genetic factors play a major role in triggering AITD, individuals with family members who develop this disease exhibit a high risk of AITD. Therefore, to get a precise answer to the question asked by individuals with AITD "Will my daughter or my sister also get this disorder?", the Thyroid Hormones Event Amsterdam (THEA) score was designed and applied for predicting AITD risk in healthy female subjects who had at least one relative with AITD based on the various baseline characteristics. This THEA score performs accurately and seems to be useful for young women of AITD families[50]. However, this THEA score still needs to be further validated externally.

In addition, for a given genetic risk factor in AITD, epigenetic modifications mediated by DNA methylation[51], histone modifications[52], and noncoding RNAs[53] may be necessary to trigger AITD. However, the promoting mechanism of such epigenetic modifications in AITD have not been fully elucidated, and therefore, more research should be done to further investigate their roles in AITD pathogenesis and to develop better diagnostic, prognostic, and therapeutic tools. Some environmental factors may induce corresponding epigenetic modifications, and subsequently trigger AITD in genetically susceptible individuals, indicating that epigenetic modifications seem to narrow this gap between genetic and environmental factors[54, 55]. Several AITD-related environmental factors have been confirmed, such as iodine status, smoking, alcohol intake, selenium supplementation, vitamin D deficiency, infections, stress, and drugs[47]. Thus, preventive interventions, namely, the modulation of exposure to particular environmental risk factors, may diminish the corresponding risk in individuals at risk for developing AITD. However, there are few effective preventive interventions to diminish this risk, and these few options are not always feasible[47].

As a result of the interaction between the above various factors, the balance of immune homeostasis is disrupted, inducing a loss of tolerance toward thyroid-specific autoantigens and finally the onset of AITD[56]. Effector T cells and their secreted cytokines contribute greatly to the pathogenic development of HT and GD[57, 58]. Traditionally, Th1/Th2 cell imbalance is viewed as the main driver of autoimmunity in AITD. Th1 cells may induce apoptotic pathways in thyroid follicular cells by secreting IFN-γ and IL-2, resulting in the destruction of thyroid cells. Th2 cells, which mainly produce IL-4, IL-5, and IL-13, may induce thyroid growth and overactivity by enhancing TSAbs release[59, 60]. In addition, numerous recent studies have demonstrated the pathogenic functions of IL-17 and Th17 cells and Th17/Treg imbalance in both HT and GD[61]. This is important for future research to discover Th17-related therapeutic targets.

Accurately diagnosing GD or HT is important, and this mainly relies on the measurement of serum levels of thyroid stimulating hormone (TSH), free thyroid

hormones (FT3, FT4) as well as the corresponding autoantibody levels. In addition, cytological examination, thyroid ultrasonography, and radiological evaluation may be needed in some cases[62, 63]. If a definitive diagnosis was established, the most appropriate patient management decision could be made. For GD treatment, mainly including thyroidectomy, radioiodine therapy, antithyroid drugs, and β-blockers, there have been no major changes in recent years[62]. For HT treatment, oral administration of a synthetic hormone is used to control hypothyroidism. In addition, diet management is advised[63]. Although these available treatments are effective for HT and GD, there are still some limitations. Thyroid hormone substitution therapy in HT does not target the disease process[64]. Available treatments performed in GD may have the potential to cause some side effects[62, 65]. Therefore, the clinical management of AITD remains an active area that requires further investigation, especially by improving understanding of its pathophysiology to discover therapeutic approaches targeting the underlying autoimmune process.

THE CONCOMITANT PRESENCE OF T1DM AND AITD

The occurrence of one autoimmune disorder enhances the risk for the development of others. Therefore, the coexistence of two or more autoimmune endocrinopathies is termed autoimmune polyendocrine syndrome (APS). However, sometimes there may be additional (non)glandular autoimmune disease(s) present[66]. There are two major types of APS, including juvenile type I and adult APS with three variants or subtypes (type II to IV)[66, 67]. An economic evaluation of the costs for patients with APS in Germany has shown that T1DM is the main cost driver in APS[68]. APS type III, encompassing T1DM and AITD (HT or GD), is the most prevalent APS type, and it can often be associated with other (non)glandular autoimmune disorders, excluding Addison's disease[69, 70]. Various studies have observed a higher rate of thyroid disorder among T1DM patients compared with the general population, suggesting that AITD represents the most prevalent autoimmune disorder concomitant with T1DM[5, 71, 72]. Existing data show that approximately one-third of T1DM individuals develop AITD within a few years, and this proportion increases up to 50% in anti-TPO autoantibody-

positive T1DM individuals. Additionally, the incidence of HT among T1DM individuals is relatively higher than that of GD[73, 74]. Conversely, the prevalence of T1DM is also enhanced in patients with HT or GD, and the incidence of T1DM in HT individuals is relatively higher than that in GD individuals[75, 76].

As described above, both T1DM and AITD are common organ-specific autoimmune disorders, and a complicated interaction between genetic factors and environmental stimuli, together with various immune events or epigenetic factors, induces the autoimmune process to destroy the target tissue (the β-cells in T1DM and the thyroid in AITD) (Figure 1). While differences in the pathogenesis responsible for both disorders persist, the relatively high concomitant presence rate of T1DM and AITD in the same individual or family indicates that these two diseases may share pathogenic factors within the induction of the corresponding autoimmune process[77]. Various genes have been confirmed to contribute to the risk of both T1DM and AITD; these are referred to as joint susceptibility genes for APS type III (Figure 1)[73, 77-79]. Among these susceptibility genes, *HLA* genes remain the most important contributor[73, 77]. Based on the interaction with susceptibility genes, environmental factors are necessary to trigger autoimmune responses in both T1DM and AITD. It has been shown that infection (such as *Helicobacter pylori* infection), vitamin D deficiency, as well as multiple chemokine (C-X-C motif) ligands could confer susceptibility to both diseases[77]. Therefore, the combined influence of these susceptibility risk factors may stimulate the corresponding autoimmune processes in various organs of the same individual or in families (Figure 1). As there may be a rather long time interval between the first occurrence of one autoimmune endocrinopathy and the other, long-term monitoring and regular evaluation of patients and their relatives is warranted, such as the detection of associated autoantibodies[80] and thyroid ultrasound[81].

ULTRASONOGRAPHY APPLICATION IN AITD

As it is noninvasive without known detrimental bioeffects and affordable, ultrasound has been widely applied in the clinic for decades. Low-resolution B-mode ultrasound was first introduced for thyroid imaging in 1967[82], and ultrasonography is currently

considered crucial in the diagnosis and management of thyroid disorders, including AITD[81, 83].

Ultrasonography in HT

As mentioned above, the cellular and humoral immunity involved in the development of HT results in morphologic and microscopic changes in thyroid tissue, such as thyroid enlargement, lymphoplasmacytic infiltration, fibroplastic proliferation, lymphatic follicular formation, calcification, vascular proliferation, and parenchymal atrophy[63]. These changes influence the ultrasonographic characteristics of HT. Generally, a moderate grayscale uniform echo image, with a higher signal compared to the surrounding muscles, can be observed in the structurally normal thyroid. As a result of thyroid infiltration in HT, a heterogeneously hypoechoic thyroid can be observed, and thus, this hypoechogenicity can be used for clarifying diagnosis[84, 85]. In addition, pseudonodules and inhomogeneous parenchyma can also be observed, which could be due to fibroplastic proliferation[86].

However, the sonographic appearances detected in HT vary greatly and may be indistinguishable from other thyroid disorders[87, 88]. Therefore, in some atypical cases, multiple sonographic characteristics obtained from various ultrasound imaging technologies should be considered. The vascularity type of “focal inferno” observed by color Doppler ultrasound is a characteristic of focal Hashimoto's thyroiditis (FHT), which is a special form of HT, and this is crucial to determine the corresponding treatment strategy[89]. In anti-TPO autoantibody-positive euthyroid subjects, comprehensive parameters obtained by ultrasound and power Doppler ultrasound exhibited a diagnostic accuracy of 87.2%, sensitivity of 90%, specificity of 84.8%, negative predictive value (NPV) of 90.7%, and positive predictive value (PPV) of 83.7% for the diagnosis of HT[90]. The cutoff value for thyroid tissue elasticity obtained from real-time ultrasound elastography for diagnosing HT showed 96% sensitivity and 67% specificity in adults[91], as well as 97.4% sensitivity and 100% specificity in children[92]. Based on ultrasound 2D shear-wave elastography, thyroid stiffness measured by shear-wave dispersion performed somewhat better in diagnosing HT than thyroid viscosity

measured by shear-wave dispersion[93]. Compared with conventional ultrasound examination, high-frequency ultrasonic elastography exhibited a significantly higher diagnostic accuracy of HT (sensitivity, 92.16%; specificity, 92.86%; NPV, 86.67%; PPV, 95.92%)[94]. A recent meta-analysis indicated that ultrasound-based shear wave elastography plays an important role and should be encouraged for use in diagnosing pediatric HT[95].

In addition, ultrasound acquisition and interpretation are highly subjective and somewhat operator dependent, even irreproducible in some cases[96]. To avoid subjective differences, a computer-assisted diagnostic system based on feature extraction and classification as well as a machine learning algorithm was proposed to provide objective and reproducible interpretation results in the diagnosis of HT, yielding a diagnostic accuracy of 80%[97], 85%[98], and 79%[99]. Recently, artificial intelligence (AI)-aided diagnosis of thyroid disorders has attracted growing interest[100, 101]. A convolutional neural network-based computer-aided HT diagnostic system was evaluated and validated in a large number of samples, including 39,280 ultrasonic images from 21,110 individuals. The results show that this strategy significantly improved the radiologists' diagnostic efficiency of HT, as it exhibited high performance (89.2% accuracy, 89% sensitivity, and 89.5% specificity)[102]. A later report in 2022 developed a deep learning-based diagnostic system for HT (HTNet) through training and testing in a larger number of samples, and HTNet significantly exceeded the performance of radiologists in terms of accuracy and sensitivity. The corresponding diagnostic performance of HTNet can be further improved by integrating serologic markers[103]. Therefore, these computer-assisted ultrasound diagnostic systems based on novel AI show promising prospects in HT management and thus could be tested in prospective clinical trials.

Cervical lymph nodes (CLNs) are often observed in HT patients[104]. Fine needle aspiration biopsy (FNAB), an invasive intervention, has been regarded as the gold standard to diagnose, differentiate, and recognize CLNs as true nodules or pseudonodules[105]. To avoid the use of unnecessary invasive biopsies,

sonoelastography should be applied, as it can detect true thyroid nodules with a similar accuracy and sensitivity to FNAB[106]. An enhanced number of enlarged CLNs without a significant increase in lymph node size was observed on the sonographic images of HT patients[107], and an enhanced frequency of CLNs with abnormal ultrasonographic characteristics has been observed in HT patients[108]. Therefore, further understanding of the sonographic characteristics of CLNs in HT patients may be useful to improve the diagnosis of HT and avoid unnecessary invasive tests.

In addition, thyroid nodules (TNs) can be frequently detected among HT patients, and these nodules often exhibit poor uptake of radioisotopes, indicating the possibility of malignancy and suggesting a possible association between HT and thyroid cancer[109, 110]. However, whether HT increases thyroid cancer risk in individuals with TNs is controversial and remains to be defined[111, 112]. Therefore, to avoid overtreatment with surgery in HT patients with TNs without any other evidence of malignancy as well as to predict the malignancy risk of these TNs accurately, various ultrasound-based diagnostic classification systems, which have been developed for differentiating benign and malignant TNs, may represent a critical role in detecting malignant TNs in HT individuals[113-116]. Moreover, in some cases with difficult diagnoses, ultrasound-guided FNAB can be used as an effective, less-invasive approach to confirm the nature of the lesion and propose the most beneficial/optimal treatment[117, 118]. For the treatment of benign TNs in HT patients, ultrasound-guided microwave ablation shows a promising trend[119].

Ultrasonography in GD

As described above, autoantibodies against TSHR (TSAbs) drive GD pathogenesis. However, the role of TSAbs in GD is different from that of autoantibodies causing tissue damage in many other autoimmune disorders. TSAbs stimulate the thyroid and increase the production and secretion of thyroid hormones, therefore causing goiter and hyperthyroidism[62]. Apart from clinical presentations and laboratory findings, Doppler ultrasound measuring thyroid blood flow is widely applied in diagnosing GD[120]. However, it should be noted that the application of ultrasound in GD management,

which mainly focuses on academic interest, has not gained much clinical importance thus far compared with that of some other thyroid disorders, such as thyroid cancer[81, 121].

Features of an increased thyroid gland volume, diffusely low thyroid echogenicity as well as hypervascularity have been shown in GD[121, 122]. At variance with the hypoechogenicity resulting from diffuse lymphocytic infiltration in HT as described above, the hypoechogenic pattern observed in GD may result from decreased colloid content with enhanced cellularity and a decrease in the cell-colloid interface and/or from enhanced blood flow[122, 123]. Alternatively, it can be said that hypoechogenicity is not specific for HT, as it can also be observed in GD. Therefore, it has been shown that conventional grayscale ultrasound exhibits a high specificity with low sensitivity in diagnosing and differentiating GD and HT, and it is difficult to differentiate between both disorders using conventional grayscale ultrasound alone as a result of those significant overlaps in ultrasonographic images[124].

During the late 20th/early 21st centuries, Doppler ultrasonography, including color Doppler and power Doppler, has been widely studied to diagnose, evaluate, and manage GD, and the characteristic intense Doppler flow referred to as the "thyroid inferno" pattern has been well defined in this disease, yielding a high specificity in differentiating GD from other triggers of hyperthyroidism[125-130]. However, at that time, little effort was made to emphasize the role of Doppler ultrasonography in GD, leading to its underutilization in diagnosing this thyroid disorder. Therefore, a call to include an ultrasound protocol with Doppler patterns in the clinical diagnosis of GD was raised in 2009[131]. Since then, various methods based on Doppler ultrasonography have been widely and further investigated for their roles in GD management. The diagnostic utility of the peak systolic and/or end-diastolic velocities (PSV and EDV) in the superior and/or inferior thyroid artery measured by color Doppler ultrasonography is comparable to the performance of TSAb and Tc-99m pertechnetate uptake to differentiate GD from painless (or silent) thyroiditis[132, 133]. Compared to EDV, PSV is a more useful parameter in differentiating GD from HT[88]. Although thyroid ultrasound

is less accurate than both autoantibody immunoassays and thyroid scintigraphy in diagnostic testing for Graves' or non-Graves' hyperthyroidism, the "thyroid inferno" pattern shows a high PPV toward GD[134]. However, as these methods are highly operator-dependent and subjective, the interobserver variability as well as the difficulty in quantifying the corresponding results objectively remain their major limitations. Therefore, a newly developed analysis software that can quantify color Doppler signals, entitled "Color Quantification" (CQ), has been introduced. The results show that the increased CQ values help diagnose GD, and therefore, the CQ technique exhibits promise in diagnosing GD[135]. In addition, a new-generation Doppler designed for improving diagnostic sensitivity, microvascular ultrasonography (MVUS), has also been tested regarding its ability in the differential diagnosis of GD and HT[136] or destructive thyroiditis[137] in a quantitative and real-time manner with low intra- or inter-observer variability. In addition, some tests analyzing the ability of shear-wave elastography in diagnosing GD show that it can be applied as a complementary technique to facilitate the diagnosis of GD[138] or the differential diagnosis of GD and HT[139].

Apart from the diagnosis or differential diagnosis of GD, ultrasound contributes a lot to treat and manage this thyroid disorder. The sonographic appearance of the thyroid gland can be used to classify GD into different clinical courses and autoimmune activities[140-142]. Therefore, color pixel density calculated based on the color-flow maps obtained with color duplex ultrasonography can be used to evaluate the optimal dose of antithyroid drugs to maintain euthyroid status in GD[143]. In addition, it is important to predict outcome in GD patients after drug withdrawal. Thus, color Doppler ultrasonography may be a useful tool to detect a relapsing course of hyperthyroidism and, therefore, facilitate the offering of an adequate therapeutic approach[126, 128]. As described above, thyroidectomy may need to be performed in some GD patients, and preoperative color Doppler sonography evaluating the superior thyroid artery may be useful to identify those individuals who are more prone to bleeding intraoperatively[144]. Concurrent differentiated thyroid cancer occurs in pediatric GD

patients, and it has been suggested that ultrasound examination should be included for those with an abnormal thyroid at palpation to select patients for appropriate definitive therapy, such as thyroidectomy[145, 146]. In addition, surgery and radioactive iodine (RAI) therapy are recommended for individuals with persistent/relapsed GD[147]. However, many patients may not want to accept surgery or RAI therapy as a result of the possible risks from surgery and radiation[148, 149]. Therefore, one preliminary study applied and evaluated ultrasound-guided high-intensity focused ultrasound (HIFU) ablation as a novel manner to treat medically refractory GD, and the results show that this strategy may be a safe and efficacious method for treating persistent/relapsed GD[150]. This usefulness was confirmed based on the outcomes (specifically, disease relapse and safety) over the two years of follow-up[151].

CONCLUSION

T1DM and AITD (HT and GD) represent the two most frequent autoimmune endocrine disorders. Accumulating evidence indicates that T1DM and AITD share similar immunogenetic susceptibilities; therefore, both diseases often cluster in individuals as well as families. AITD has been the most prevalent comorbid autoimmune disease of T1DM. Thus, a timely and accurate diagnosis of AITD in T1DM patients is particularly crucial for diabetes management. For this purpose, thyroid ultrasonography exhibits a critical role in the diagnosis and management of AITD.

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