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Immunological Mechanisms Implicated in the Pathogenesis of Chronic Urticaria and Hashimoto Thyroiditis

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ABSTRACT

Autoimmunity represents the attack of the immune system of an organism against its own cells and tissues. Autoimmune diseases may affect one organ (Hashimoto thyroiditis) or can be systemic (chronic urticaria). Many factors are implicated in the pathogenesis of autoimmunity (white cells, cytokines, chemokines). Hashimoto thyroiditis has been associated with chronic urticaria in the last 3 decades in a number of clinical studies. Anti-thyroid antibodies have been documented in a proportion ranging from 10% to 30% in chronic urticaria patients in different countries from 3 continents. Two of the factors involved in the mechanism of autoimmunity are present both in the pathophysiology of Hashimoto thyroiditis and chronic urticaria. According to recent studies, IL6 is implicated in the pathogenesis of both diseases. TregsCD^{4+}CD^{25+}Foxp^{3+} cells have also been implicated in the pathological mechanisms of these 2 entities. This review offers an explanation of the clinical and statistical association between these two diseases from the pathophysiological point of view.

Keywords: CD 4+CD25+Tcells; Chronic urticaria; Hashimoto thyroiditis; Interleukin 6

INTRODUCTION

Autoimmunity-General Considerations

Autoimmunity is the response of the immune system to self-antigens.[1] The pathogenesis of autoimmune diseases involves multiple mechanisms: T-cell bypass (B-cell activation by superantigens bypassing T-cell help), T-cell-B-cell discordance, aberrant B-cell receptor-mediated feedback,[2] molecular mimicry, idiotype cross-reaction, cytokine dysregulation, dendritic cell apoptosis,[3] epitope modification,[4] cryptic epitope exposure.[5]

Autoimmune diseases can be broadly divided into systemic disorders and organ-specific or localized disorders, depending on the principal clinicopathological features of each disease. Systemic autoimmune diseases tend to be associated with autoantibodies to non-specific tissue antigens (systemic lupus erythematosus, rheumatoid arthritis, Sjogren's syndrome, cryoglobulinemic vasculitis, scleroderma, dermatomyositis). Organ-specific disorders are associated with specific tissue antigens-for example endocrinologic disorders (diabetes mellitus type 1,

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Hashimoto's thyroiditis, and Addison's disease), dermatologic diseases (pemphigus vulgaris and vitiligo), neurological disorder (myasthenia gravis), gastrointestinal (Crohn's disease, celiac disease, pernicious anemia), hematological (autoimmune hemolyticanemia, idiopathic thrombocytopenic purpura).

In recent years scientists have proposed a new concept of "immunological disease continuum", according to which immune system diseases can be seen as a spectrum of pathology from autoimmune to autoinflammatory reactions, with different and relative contributions of innate and adaptive immune responses adapted to particular cases.[6]

In the last 3 decades two conditions (chronic urticaria and Hashimoto thyroiditis) with autoimmune mechanisms were shown to have statistically significant association in some important clinical studies. This review aims to present the common mechanisms of the pathogenesis of these two apparently independent diseases, which might explain that associations.

Hashimoto Thyroiditis-Autoimmune disease

Autoimmune thyroiditis (AIT), known as Hashimoto thyroiditis (HT), is an organ-specific autoimmune disorder, characterized by thyroid invasion by lymphocytic cells, followed by follicular destruction and replacement with parenchymatous tissue, which leads to hypothyroidism.[7] The disease was first described in 1912 by Hakaru Hashimoto (1881-1934) as a new type of thyroid disorder with thyromegaly, follicular inflammation and hypothyroidism; different from hypothyroidism with thyroid atrophy (called mixedema or Ord thyroiditis). Subsequently the background of the thyroid lesion's pathogeny was recognized as immunological and thereby given the name lymphocytic, chronic, autoimmune.[8] HT together with other thyroid autoimmune disease, Graves' disease (GD), present with an incidence of 2% in general population, making autoimmunity against thyroid the most frequent autoimmune disease in humans and the prototype of autoimmune organ-specific disease.[9,13] HT affects mostly middle aged women (2-4%) and much less men (1%), the prevalence rate increases with advancing age (the maximum of incidence being between the age of 45 and 65).[10,11]

The etiology of HT is multifactorial. The main factors implicated are: anti-thyroid antibodies, B lymphocytes, T lymphocytes (particularly regulatory T cells [Tregs] and Th17), apoptosis, TNF-related apoptosis-inducing ligand (TRAIL), bystander activation, NK cells and thyroid-cell expression of HLA antigens.[11,12]

The primary antigens are thyroperoxidase and thyroglobulin. Initial investigations about the pathogenesis of HT noticed that the disease was generated by an antibody named antimicrosomal", because it affected microsomes (cellular organelles of thyrocytes). Subsequent investigations of antimicrosomal antibodies discovered the antigen: thyroperoxidase. Thus the term" antimicrosomal antibody" has changed to antithyroperoxidase (ATPO). Thyroperoxidase is an enzyme, glycoprotein attached to the thyrocyte's membrane at apical level (to the colloid). It contains 2 identical subunits of approximately 100 kDa with 834 aminoacids. It has acolloidal extracellular domain of 93 kDa. Its main role is to transforminorganic iodine (I^-) to organic iodine (I_2). The antigenic area, recognizable by antibodies, is similar to that of myeloperoxidase and that of complement control protein. Thyroperoxidase has 2 dominant epitopes, conventionally named IDR-A and IDR-B. Therefore, some authors admit only 2 types of antibodies against them. Epitopes seem to be situated very closely, being considered as a superposition. Both epitopic regions seem to be localized in the 590-622 aminoacid zones. Epitope B is sure to reside between 599-617. Epitope A is centered on lysine-phenylalanine-proline-glutamine in the positions 713-716 according to recent studies.[14] Other authors proposed that the autoimmunity directed against thyroperoxidaseis a specific polyclonal response with a minimum of 6 distinct, independent determinants[7]. ATPO serum levels are associated with the inflammation level of thyroid, their detection represents a specific method for diagnosing the disease.[15,16] Thyroglobulin is a 660 kDa glycoprotein that constitutes the storage form of thyroid hormones within the thyroid follicle. Thyroperoxidaseis an enzyme located at the apical border of the thyroid cell responsible for iodinating thyroglobulin and producing the thyroid hormones. Laboratory experiments demonstrated that thyroglobulin with a high iodine content is more immunogenic than thyroglobulin with low iodine content[17]. Human studies indicated that immune responses in the form of antibodies or Tcells decreases to minimal levels when thyroglobulin loses

iodine and restores to normal comparing to when thyroglobulin is iodinated. Different iodine content can create new epitopes and make new sites for monoclonal antibodiesaccessible.[18-21] Iodine content of thyroglobulin may also affect its proteolytic degradation, modified processing of the iodine-thyroglobulin (I-Tg) complex in antigen-presenting cells APC can generate non-iodinated cryptic pathological determinants.[22]

In recent years, more antigens implicated in the immune reactions in some particular cases of the HT have been described: Na^+/I^-symporter (NIS)[12] and pendrin.[23,24] A specific antibody for a particular form of HT (Hashimoto encephalopathy) – anti-alpha-enolase (NAE antibodies, has also been described. This antigen is represented by the amino terminal of alpha-enolase (the antigen is not localized in the thyroid).[25] In HT an increased number of activated plasma cells (proven by their ability to secrete anti-thyroid antibodies spontaneously in vitro) has been found, of which more than a half were CD79alpha+Bcells.[11] T lymphocytes play two roles in HT pathogenesis: 1) Th2 cells lead to an excessive stimulation and production of B cells and plasmatic cells, which produce antibodies against the thyroid antigens, leading to thyroiditis;2) Th1 cells activate macrophages and cytotoxic lymphocytes, which directly destroy thyroid follicular cells. Also documented in HT were Th17 lymphocytes, a different subtype of lymphocytes accounting for approximately 1% of CD4+ lymphocytes in blood serum, which are players in the orchestrating of immune responses against cellular antigens. Regulatory T cells ($CD4+CD25+^{high}Foxp3+$), which play a role in suppressing or reducing immune responses, are presented in a reduced number or possess functional deficiencies.

Apoptosis is also implicated in HT pathogenesis, given the highly significant level of thyrocytes with apoptotic molecules and proapoptotic proteins (including TRAIL) on the surface, which lead to the destruction of follicular cells. Viral infection of thyroid cells or the arrival of activated nonspecific lymphocytes in thyroid may cause local release of cytokines, which may activate local thyroid-specific T cells. Infection can also induce the expression of HLA antigens on the surface of thyrocytes, which can turn them into APC, thereby initiating a thyroid autoimmune response.[11] Other factors implicated in HT pathogenesis are genetic susceptibility and environmental factors, and interrelations between them.[13,26,27] Genetic susceptibility is suggested by familial clustering of the disease (20-30% from the siblings of affected patients will develop HT), the sibling risk ratio (about 17%) and the increased prevalence of thyroid antibodies (50%) of siblings of affected patients. Genetic studies using various techniques have correlated a number of genes involved in HT: MHC genes, which may determine cell-mediated destruction (HLA class I) or auto-antigen presentation (HLA class II); T cell immune response genes (IL2RA encodes the interleukin-2 receptor, FCRL3 affects regulatory T cell function, CTLA4 and PTPN22 regulate T cell activation), other immune response genes (CD226 represents an activating receptor on NK cells, CD40 encodes a co-stimulator of APC), and thyroid specific genes (genes encoding two thyroid autoantigens: thyroglobulin and the TSH-receptor). Non-genetic factors associated with HT can be grouped in: 1) Dietary (iodine excess, alcohol [protective], vitamin D and selenium deficiency), 2) Toxins (environmental pollutants, smoking [protective], low-dose irradiation, drugs [lithium, immunomodulators, anti-neoplastic agents]), and 3) Demographics (age, parity, female sex, large family, hygienic environment).[26,27] Iodine is best investigated among ambient factors. Iodine excess can stimulate intracellular adhesion molecule-1(ICAM-1) expression on thyrocytes, which can explain the high number of lymphocyts in thyroid. Iodine is taken up by thyrocytes, organified and stored in the thyroglobulin molecule through the enzymatic reaction of thyroperoxidase, in which free radicals of oxygen and hydrogen peroxide compounds known to signal ICAM-1 transcription are released. ICAM-1 overstimulation will lead to an accelerated thyroid's infiltration with mononuclear cells.[17] The generation of extracellular H_2O_2 by thyrocytesmay accelerate tissue damage via apoptotic/necrotic effects and the release of degraded thyroglobulin.[21] Iodine excess in the feeding of NOD.H-2^{h4} mice for 8 weeks led to an important lymphocytic infiltration of the thyroid and detection of typical histological aspects of autoimmune thyroiditis. The study demonstrated a high expression of IL6, TGF-β, IL17, and IL23. IL6 and TGF-β over-expression promoted receptor-related orphan receptor (RORγt) and RORα expression, leading to IL17 overproduction, maintaining a proinflammatory status through an increased number of Th17. High levels of IL-6

suppress the transformation of naive CD4+ T cells to Tregs leading to the low expression of Foxp3 that will suppressTh1 and Th2 cell differentiation. Thus, the functions of Tregs, Th1 and Th2 cells are inhibited in the course of HT.[28] Moreover, in other study, feeding of mice with iodine in excess induced experimental autoimmune thyroiditis with a big number of T CD4+ cells and characteristic histological lesions.[29]

Chronic Urticaria-Pathogenic Mechanisms

Chronic urticaria (CU) is a disease characterized by itchy swellings with central edema surrounded by a reflex erythema, angioedema or both, occurring daily or almost daily for at least 6 weeks, due to known or unknown causes.[30] CU affects 0.5-1% of the population and significantly modifies the quality of life.[31] CU is classified into chronic spontaneous urticaria and inducible urticaria (by physical stimulation).[30] CU is also divided into 2 subgroups: one group with proven autoimmune etiology [antibodies against FcεRIα (alpha subunit of the high affinity IgE receptor), antibodies against IgE, antithyroid antibodies including ATPO, and anti-thyroglobulin antibodies (ATGL)] and an idiopathic group, in which the existence of antibodies has not been proven.[32,33] The persistence and intensity of the symptoms are correlated in some cases with existence and titer of antibody[34].The urticarial wheal is characterized by dermal edema, vasodilatation and perivascular infiltrate, comprising CD4+ lymphocytes, monocytes, neutrophils, eosinophils and basophils. Chronic urticaria is initiated by the inappropriate activation and degranulation of mast cells, a key pathophysiological event. The autoimmune hypothesis is the most accepted hypothesis and there is circumstantial evidence supporting it: higher prevalence of thyroid antibodies in chronic urticaria, positive autologous serum skin test, identification of IgG antibody directed to the alpha subunit of the IgE receptor or IgE itself, positive association with some HLA subtypes, therapeutic responses to intravenous immunoglobulin and plasmapheresis. Moreover abnormalities in some leukocytes (basophils, mast cells) were related to the disease pathogenesis.[35] A characteristics of leukocites abnormality is basopenia, the basophils number is inversely correlated to the severity of urticaria. Also two functional phenotypes of basophils related to basophil histamine release with polyclonal autoantibodies anti–IgE (CIU-R versus CIU-NR) have been confirmed. Mast cells secrete preformed mediators (histamine, serotonin, proteases, proteoglycans) and newly-formed mediators including [TNF-α, IL6, vascular endothelial growth factor (VEGF), and platelet activating factor (PAF)]. The action of ligands such as IgG, peptides, microbial derivatives, and fragments of activated complement at the level of membrane receptors is the principal mechanism responsible for this activation.

Derangement of innate immunity in CU is implicated in the functional impairment of plasmocytoid dendritic cells (PDC) because of downregulation of TLR9. Other aspects of inflammation such as high levels of c-reactive protein (CRP) and neopterin have been demonstrated.[37] The maintenance of active inflammatory status in urticaria is also sustained by the action and higher serum levels of chemokines (C-C and C-X-C): CXCL8, CXCL9, CXCL10 and CCL12.

Clotting cascade was also involved in the pathogenesis of urticaria. The plasma of patients with urticaria contains significantly higher levels of prothrombin factor F12and severe exacerbations of urticaria are associated with a strong activation of the coagulation cascade. The resulting thrombin is a serine protease that enhances vascular permeability, activates and degranulates and induces the generation of anaphylatoxinC5a. Mast cells can be activated through non-immunological mechanisms by agonists like substance P, endorphins, enkephalins, somatostatin. These different pathological mechanisms are probably interconnected between them. They are acting together synergically or sequentially, rather than as independent cascades, in the pathogenesis of urticaria.[35-38]

Chronic Urticaria and Hashimoto Thyroiditis–Two Associated Diseases

Hashimoto thyroiditis was considered to be associated with chronic urticaria in the last 3 decades.[39] Studies performed in patients with CU detected an incidence of 10-30% of thyroid antibodies, depending on methodology and study population. The research (in Canada) published in 1983 by Leznoff et al was the first study that suggested an association between these two entities (12.1% of investigated patients with CU were positive for ATPO).[40] Another study by the same author published in 1989 which enrolled 624 patients with CU found 90 patients with thyroid autoimmunity(14%). The association was considered significant (p<0.1), considering that the number expected by chance alone

was 37.[41] Subsequent studies in patients with CU found incidences of thyroid antibodies of 11.7% in Turkey (11 patients from 84),[42] Italy (33% of patients with a known etiological cause of CU and 23% of patients with idiopathic CU),[43] Thailand (21% in patients with CU versus 9% in volunteers),[44] Mexico (55% in CU patients group, but with a small total number of patients).[45]Another investigation conducted in Turkey (2006)could strengthen this association because of a large study population including volunteers and a significant higher number of patients (frequency of thyroid antibodies in patients with CU vs. controls29.28 % vs. 5.52%; $p<0.001$).[46]

Moreover, a significant statistical association was noticed in Pakistani women patients with CU[47]. Prevalence of thyroid antibodies and autoimmune thyroiditis were significantly higher in southern Italy in an area with moderate iodine deficiency in patients with CU versus controls (22% vs. 6.5 % for antibodies; 18.5% vs. 1.8% for autoimmune thyroiditis).[48] Autoimmune thyroiditis was also strongly associated with CU in Lebanon(ATPO incidence in CU patients versus ATPO in controls 17.7 vs. 8.7; $p<0.01$).[49] The incidence of autoimmune thyroiditis in a group of 115 Brazilian patients with CU was 16.5% and the risk of developing angioedema (a more severe form of CU) was 16.2 times higher in patients with CU and autoimmune thyroiditis vs. patients with CU only.[50] 11 patients from 40 with CU enrolled in an investigation in Japan presented concomitantly autoimmune thyroiditis.[51] High levels of ATPO were found in18,6% of patients with CU in a Romanian cohort (mostly women) in a study published in 2014(39 from 210).[52] An unpublished study that evaluated patients from the Bucharest region (Romania) followed the appearance of these two comorbidities in two independent groups: a group of patients with HT (1450 patients included) and a control group (1400 patients) over a period of 20 years.CU was presented in 56 patients in the HT group (prevalence 3.89%) versus 14 in the control group. The difference (χ^2=25, 47; $p<0,001$) was highly significant, suggesting a connection between these two diseases. There was a strong prevalence of female sex (6:1) (courtesy of Dr Peretianu Dan).

The biggest study that evaluated CU and its association with autoimmune diseases included 12778 patients with CU and 10714 controls over a 17-year period. Thyroid diseases (including autoimmune thyroiditis) were the most frequent comorbidities, 9.8% (1257) presented hypothyroidism in the CU group compared to the control group 0.6% (67) ($p<0.0005$) Hyperthyroidism was less frequent than hypothyroidism in this study, but still more significant in CU patients versus controls (2.6% and 0.09%, respectively; $p<0.0005$). The risk of having hypothyroidism or hyperthyroidism was significantly higher both in women and men with CU as compared with controls. Significant differences between CU patients and controls were noticed when the authors evaluated thyroid antibodies frequencies. High levels of serum ATPO was present in 508 women patients in CU groups, 5 in controls (6% vs. 0, 3%, $p<0.0005$) and in 90 male patients with CU vs. 49 in controls (2.1% vs. 0.5%, $p<0.0005$). The same situation goes for ATGL, which was above normal in 117 women patients in the CU group vs. 1 in the control group (1.4% vs 0.1%, $p<0.0005$) and in 21 male patients vs. 4 controls (0.5% vs. 0.04%, $p<0.005$).[53]

Common Immunopathological Mechanisms in Chronic Urticaria and Autoimmune Thyroiditis

Interleukin 6

CU pathogenesis is extremely complex, implicating many mechanisms, only a part of them being known. Recent studies on both human and murine subjects questioned the implication of IL6.[54-56] Human IL6 consists of series of phosphoglycoproteins of molecular mass from 21 to 45 kDa with roles in the proliferation, differentiation and specialization of hepatocytes, fibroblasts, keratinocytes, epithelial cells, B cells, T cells, NK cells, megakaryocytes, and neuronal cells. IL6 is a cytokine produced in local sites (skin lesions), but it can be found in high levels in peripheral circulation, playing a key role in orchestrating a systemic response to a local injury. IL6 has synergies with others cytokines like IL1 in the activation of local immune system cells in local cutaneous tissue.[57] IL6 is capable of increasing the endothelium permeability in vitro, a fundamental mechanism in the pathogenesis of urticaria.[58] A small study conducted in the 2007 demonstrated a significant higher serum level of IL6 in patients with CU vs. controls.[59] A second study from the same team strengthened the association between IL6 and chronic urticaria. The study included 58 patients with CU, having different severities, and 30 controls. The serum level of IL6 was significantly higher in patients with CU than controls (median: 1.85 vs. 1.1 pg/mL; $p<0.001$). Also, differences were

observed in plasma IL6 concentration between the CU patients regardless of the level of severity (mild, moderate, severe) (median: 1.2 vs. 1.9 vs. 3.3 pg/mL, respectively; $p<0.05$ and <0.001) and disease activity. IL6 levels diminished with the remission of urticaria.[54] Same correlation between IL6 level and disease severity were noticed by another team.[60] High levels of IL6 were measured in patients with particular types of urticaria like delayed pressure urticaria.[56,61] IL6 was found in high levels in studies investigating Hashimoto thyroiditis, where it was correlated with an increased number in Th22, which in turn were correlated with ATPO levels, suggesting a connection between this interleukin and HT.[62-64]

Regulatory T Cells

Tregs are T lymphocytes with an immunosuppressive phenotype. There are several types described: CD4+CD25+ Treg-cells, IL-10-secreting Tr1 cells, TGF-β -secreting Th3 cells, CD8+CD28− T-cells, CD8+CD122+ T-cells, γ δ T-cells and NK T-cells. Some Tregs are naturally produced as functionally distinct populations (nTreg), whereas others are adaptively induced from naive T-cells under the influence of a particular cytokine milieu (iTreg).[65] $TregFoxp_3CD_{4+}CD_{25+}$ cells show recognized suppressor properties on effector immune cells. This mechanisms include direct actions like production of anti-inflammatory cytokines (IL10, IL35), sequestration of cytokines essential for cell growth (IL2), surface expression of cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) which is an immunosuppressive molecule, utilization of the perforin-granzyme pathway to kill activated targets or tumor cells and indirect actions like modulation of the dendritic cells function.[66] Reduced number or functional properties of Tregs were associated with a variety of autoimmune diseases by favoring autoimmune mechanisms.[67] These modifications were noticed in systemic lupus erythematosus, Wegener's granulomatosis, Sjogren's syndrome, and rheumatoid arthritis. The etiology and exact mechanism of this defect are elusive.

Recent studies demonstrated an important connection between Tregs and Th17, main pathogenic effector subset involved in the induction of inflammation and autoimmunity. TregsFoxp3+ are not terminally differentiated and they can be converted into Th17 in the context of an inflammatory cytokine milieu. Recent discoveries demonstrated that the balance between TGF-β and IL-6 can induce differentiation of Tregs/Th17 through the antagonist competition of Foxp3 and RORγt and can indicate the propensity of Tregs to Th17 in the right context. Activation of naive T cells in the presence of TGF-β results in the generation of Foxp3+Tregs, whereas the combination of IL-6 and TGF-β promotes the generation of Th17 cells, suggesting that both T-cells subsets may differentiate from the same precursor.[68] Murine and human studies published in the last years implicated these cells in the pathological mechanisms of the2 diseases presented in this review. A recent study that included patients with CU and controls demonstrated a significant low percentage of T CD4+CD25+Foxp3+ cells in patients with CU vs. controls.[69]The same difference was remarked when the level of this cell was compared between patients with autoimmune urticaria (AU), idiopathic chronic urticaria and healthy controls, with normal values in controls and the lowest values of TCD4+CD25+Foxp3+ cells in the patients with AU.[70] The decreased suppressive capacity of T CD4+CD25+Foxp3+ cells and the decreased number of the cytokines produced by them were demonstrated in another study that compared patients with CU vs. controls.[71] Defects of Tregs were also discovered in HT. An experimental studyusing$NOD.H\text{-}2^{h4}$ mice (prone to develop iodine-induced autoimmune thyroiditis -AIT), that were divided in 2 groups (one fed with a high iodine intake and one control), revealed a significantly reduced percentage of T CD4+CD25+Foxp3+ cells in the group with iodine intake, which can suggest its role in the onset and development of HT.[72] Dysfunctions of Tregs were noticed in studies in humans. A study evaluating patients with autoimmune thyroid diseases (HT, GD), controls and patients with Down syndrome found no differences regarding the frequency of Tregs as a percentage of CD4+ cells between patients and controls. The authors noticed that Tregs from patients with autoimmune thyroiditis were partly dysfunctional comparing with those from healthy controls.[73] Another study investigated Tregs, Th17 and the dynamics of the relationship between them in patients with HT and controls. Patients with HT presented significantly lower concentrations of Tregs (1.64±0.49 vs.3.90±1.36 %, $p<0.01$) and higher of Th17 (1.59±0.57 vs. 0.40±0.15 %, $p<0.01$) in HT patients vs. controls. There was a tendency of reducing Tregs and increasing Th17 as HT increases in severity and this imbalance was correlated with thyroid antibodies levels.[74]

Autoimmune thyroiditis represents the most important comorbidity in patients with CU; there are significant statistical associations between these two conditions. Iodination of food led to an increase inIL6 serum levels with consecutive demonstration of its role in autoimmune thyroid pathology. Recent studies demonstrated the implication of IL6 in the development or aggravation of CU. Lower serum levels and functional defects of T CD4+CD25+Foxp3+ cells are also implicated in the pathogenesis of these two diseases. Future investigations to include groups of patients with CU and HT with/without CU with the parallel studying of IL6, Tregs and iodine levels are necessary to confirm these theoretical observations.

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