The aggregation between AITD with rheumatologic, or dermatologic, autoimmune diseases.

Poupak Fallahi[1], Giusy Elia[2], Francesca Ragusa[2], Ilaria Ruffilli[2], Stefania Camastra[2], Claudia Giusti[2], Sabrina Rosaria Paparo[2], Debora Gonnella[2], Yehuda Shoenfeld[3-5], Silvia Martina Ferrari[2], Alessandro Antonelli[2].

[1] Department of Translational Research of New Technologies in Medicine and Surgery, University of Pisa, Pisa, Italy; tel: +39-050-2212111, fax: +39-050-993472;

[2] Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy; tel: +39-050-992318, fax: +39-050-993472;

[3] Zabludowicz Center for Autoimmune Diseases, Sheba Medical Center, Tel-Hashomer, Israel, tel: +972-3-5308070; fax: +972-3-5352855;

[4] Sackler Faculty of Medicine, Tel-Aviv University, Tel-Aviv, Israel;

[5] I.M. Sechenov First Moscow State Medical University of the Ministry of Health of the Russian Federation (Sechenov University).

List of authors:

Poupak Fallahi	poupak.fallahi@unipi.it
Giusy Elia	e.giusy_87@hotmail.it
Francesca Ragusa	francescaragusa86@gmail.com
Ilaria Ruffilli	ilaria.ruffilli@gmail.com
Stefania Camastra	stefania.camastra@unipi.it
Claudia Giusti	claudiagiusti94@gmail.com
Sabrina Rosaria Paparo	sabrinapaparo@gmail.com
Debora Gonnella	debora.gonnella@icloud.com
Yehuda Shoenfeld	Yehuda.Shoenfeld@sheba.health.gov.il
Silvia Martina Ferrari	sm.ferrari@int.med.unipi.it
Alessandro Antonelli	alessandro.antonelli@med.unipi.it

Corresponding Author:
Alessandro Antonelli, MD
Director: Immuno-Endocrine Section of Internal Medicine
Professor of Medicine
Head, Laboratory of Primary Human Cells
Department of Clinical and Experimental Medicine
University of Pisa, School of Medicine,
Via Savi, 10, I-56126, Pisa, Italy
Phone: +39-050-992318
Fax: +39-050-993472
e-mail: alessandro.antonelli@med.unipi.it

Abstract

Autoimmune thyroid diseases (AITD) are organ-specific autoimmune disorders mediated by Th1 lymphocytes, whose main clinical presentations are Hashimoto's thyroiditis (HT), or Graves' disease (GD). HT, GD, thyroid autoantibodies and thyroid dysfunctions have been shown in systemic rheumatologic diseases (as Sjögren's syndrome, systemic lupus erythematosus, rheumatoid arthritis, systemic sclerosis, or cryoglobulinemia). New associations of AITD with other autoimmune diseases are being discovered, for example with psoriatic arthritis and dermatological diseases. Several investigations suggest the importance of a shared genetic susceptibility and of environmental factors in patients with AITD and associated systemic autoimmunity. A major Th1 autoimmune response occurs in the initial, and/or active phases of organ-specific autoimmune disorders and/or systemic rheumatologic diseases with increased serum, or tissue, expressions of the Th1 chemokine CXCL10. Thyroid dysfunctions might have an important clinical impact, so a periodic thyroid screening in women with systemic or dermatological autoimmunity, overall in presence of thyroid autoantibodies is suggested.

Keywords: Autoimmune thyroid diseases, Systemic autoimmune diseases, Dermatological autoimmune diseases, Chemokines, Cytokines.

Word Count: Text with references: 6286

1. Introduction

Hashimoto's thyroiditis (HT), or Graves' disease (GD), are autoimmune thyroid disorders (AITD), classified as organ-specific autoimmune diseases mediated by T lymphocytes, sharing similar origins of an immune attack against thyroid (1), whose clinical hallmarks are hypothyroidism, or thyrotoxicosis, respectively.

The well-known Whickham Survey conducted a prospective study on 2779 patients reporting a prevalence of AITD of approximately 5% (2); nevertheless, the frequency of anti-thyroid antibodies (ATA) in the general population might be even higher (3). The incidence rates of HT and hypothyroidism are increasing (4), also due to more accurate diagnostic procedures that allow to determine also borderline or mild cases (5-7).

The HT prevalence varies geographically differing with race, as well as between areas of sufficient or deficient iodine (3), furthermore it is more frequent in advanced age, and in women (with a ratio F/M of about 6/1) (3).

It is frequent to find other organ-specific autoimmune attacks in AITD patients such as type II autoimmune poly-glandular syndrome; the association between Type I diabetes (T1D) and AITD is the most common (8,9).

A study reported that the aggregation between AITD with non-thyroidal autoimmune diseases (NTAD) varies according to the onset of the AITD and another variable seems to be the presence of Down's syndrome (DS). Celiac disease and T1D were more frequent in children with respect to adults. A shift from HT to GD occurs in a sequential manner in children with AITD, with a frequency that seems to be higher in children with DS than in those without (10).

Moreover, these autoimmune associations increase with age, and adults with HT have a higher prevalence and a higher risk of concomitant NTAD (11). Therefore, ATA and thyroid function abnormalities were commonly found in systemic autoimmune disorders [Sjögren's syndrome (SS), systemic sclerosis (SSc), systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), psoriatic

arthritis (PsA)] (12-14), as well as in dermatologic autoimmune disorders, [vitiligo (VL) (15) and psoriasis (PSO)] (16).

Here, we review the aggregation of AITD with systemic and dermatologic autoimmune disorders.

2. Rheumatologic Autoimmune Diseases

2.1 Sjögren's syndrome

Salivary and lachrymal glands are the targets of SS in which a progressive lymphocytic and plasma cell infiltration occurs, followed by autoantibodies release that leads to xerostomia and kerato-conjunctivitis sicca (17).

The association between AITD and SS, mainly in women, is the most frequent one of AITD and rheumatic disorders (18,19).

The frequency of circulating thyroid hormone autoantibodies (THAb) was studied in primary SS (pSS), RA, HT and GD patients. Most of the SS or RA cases positive for THAb were negative for thyroglobulin antibodies (AbTg), while the opposite was true for the two AITD. These findings could be explained by a molecular similarity between extra-thyroid connective proteins (specifically linked to primary SS and RA) and iodinated regions of Tg (20).

One hundred and thirty-seven pSS patients were investigated, in another study, to evaluate the prevalence of thyroid dysfunction and autoantibodies with a longitudinal follow-up of 1-16 years, *vs.* one hundred and twenty controls (21). The frequency of thyroid abnormalities was higher in pSS patients with respect to controls (30% *vs.* 4%), as were anti-thyroid peroxidase antibody (AbTPO) and AbTg (11% *vs.* 3%). At follow-up 12/97 pSS patients manifested thyroid dysfunction (21).

In a retrospective study (with a long-term outcomes: 25 years) including 152 pSS patients, 75 (49.3%) developed other autoimmune diseases; the most common were AITD (15.8%) (22).

A similar autoimmune response against thyroid cells and the salivary gland cells is suggested by the histopathology, that showed focal or diffuse infiltration of T cells in thyroid, or salivary glands (18). High frequency of haplotypes DR3 and HLA-B8 in Caucasian patients affected by AITD and pSS suggest their involvement in these diseases (18).

The frequency of pSS was ten times higher in subjects having AITD, and that of HT nine times higher in pSS subjects, in comparison to the controls (23).

Another study found that AITD were frequent in SS patients, with hypothyroidism being the most common dysfunction (14%), while the prevalence of hyperthyroidism was lower (1.8%) (24).

In a further study, conjunctivitis sicca and xerostomia, were observed in about 32% of the patients affected by HT (25).

Moreover, the risk of pSS increased in a significant manner in female patients with thyroid diseases, in particular in those in their mid-forties to mid-sixties, in a longitudinal study from Taiwan (26).

A recent retrospective study showed a frank thyroid poly-autoimmunity in 15.7% of patients with SS and latent one in 5.6%. AITD and SS shared common pathophysiological characteristics, both were indeed characterized by lymphocytic infiltrates, in particular by CD4+ T lymphocytes and B cell (17). Epithelial cells and chemokines cover an important role in the inflammation, in fact it was found that chemokine (C-X-C motif) ligand 10 (CXCL10) was a marker of inflammatory response in AITD, and that CXCL9 and CXCL10 production by epithelial cells led to salivary gland damage (17).

The association between SS and autoimmune thyroiditis (AT), or GD has been recently showed in two different large studies with appropriate internal control groups (that evaluated >3000 patients with AT, or GD *vs.* age and gender matched controls) (27,28).

On the basis of the cited studies, the major part of the Authors suggested a regular screening of

thyroid function and autoantibodies in SS women, and that is also necessary to evaluate the coexistence of SS in AITD women (23).

2.2 Systemic lupus erythematosus

SLE is a systemic autoimmune disorder whose characteristics are chronic inflammation in combination with the presence of autoantibodies against several antigens, such as dsDNA, Ro/SS-A, La/SS-B etc. (29). Different studies found that SLE and thyroid autoimmunity are associated (30–32). Discrepant results were reported regarding the prevalence of different ATA (33). However, a high prevalence of hypothyroidism (clinical/subclinical) was described, in a vast range of variability (from 4% to 21%) (34); while discordant results arose about hyperthyroidism and GD (34).

In a retrospective Taiwanese nationwide cohort study, patients with a new diagnosis of SLE, were examined for ten years and data about prognoses of hypothyroidism, hyperthyroidism, and AT were collected (35). The Authors found that the rates of thyroid diseases and hyperthyroidism were significantly lower in SLE patients *vs.* matched controls; the risks of hypothyroidism and AT, among SLE patients, were different in the presence of overlap syndrome (35).

The discrepant results observed in the literature could be due both to methodological bias (for example the absence of an appropriate control group), or environmental factors (for example, iodine deficiency).

However, a study evaluated the frequency of thyroid disorders in 213 patients with SLE *vs.* 426 sex- and age-matched controls, belonging to a geographic area, with a similar iodine intake (13). Mean thyroid-stimulating hormone (TSH) and AbTPO levels were higher in SLE female patients *vs.* controls, and a higher prevalence of hypothyroidism (clinical and subclinical), and GD were demonstrated (13).

Another Chinese retrospective case-controlled study, evaluated patients with SLE plus AITD *vs.* SLE patients without AITD (age and gender matched), reporting that serositis, anti-dsDNA+ and low complement 3, were associated with SLE plus AITD. Serositis resulted to be a risk factor for AITD, so it was proposed that AITD may be took into account in serositis SLE patients (36).

Two different large studies, with appropriate internal control groups, have shown the association between SLE and AT, or GD, by evaluating more than 3000 patients with AT, or GD *vs.* age and gender matched controls (27,28).

Furthermore, the prevalence of thyroid cancer (TC) in 153 SLE patients was compared with that in two control groups (gender- and age-matched): 1) 459 subjects extracted by a iodine-deficient area; 2) 459 subjects extracted by a iodine-sufficient area (14). The levels of circulating TSH, AbTg and AbTPO antibodies, as well as the prevalence of hypothyroidism, were significantly higher in SLE. Five patients with papillary TC (PTC) were found in SLE, while no PTC was detected in the iodine-deficient groups controls, and only one case in the iodine-sufficient controls. Thyroid autoimmunity was observed in 80% of SLE patients with confirmed TC, whereas only in 31% of SLE patients without TC (14). These findings suggested a higher prevalence of PTC in SLE, especially in presence of thyroid autoimmune disorders (14). Consequently, during the follow-up of these patients, a careful surveillance of the thyroid was suggested (14).

Although the pathogenic mechanism of this association is unknown, genetic influence was suggested by a study conducted on 35 families with SLE plus AITD, in which the 5q14.3-q15 gene was identified as major *locus* of susceptibility both for SLE, such as AITD (37).

Another study found that the frequencies of HLA-B8 and DR3 were higher in SLE and HT patients (38).

2.3 Scleroderma

Progressive SSc (or diffuse SSc) is a disease of the connective tissue whose etiology is unknown. Its main features are multi-organ fibrosis, vascular abnormalities, and autoimmunity (39).

The aggregation of SSc with thyroid fibrosis (40), hypothyroidism (40–43), and thyroid autoimmunity (40–43) was indicated by several papers, but many discordant results have been also reported. For other thyroid disorders such as GD (44,45), only anecdotal reports are found in the literature. The discrepancies observed could be due to the fact that most of the studies did not have a proper control group (40–42,46). Moreover, none considered the iodine intake of the studied population, which is a major risk factor for thyroid diseases.

However, a study investigated the prevalence of thyroid disorders and AbTPO in 202 subjects with SSc, *vs*. 404 controls (gender- and age-matched) with similar iodine intake, using a complete clinical evaluation. The risk of hypothyroidism (subclinical and clinical) and thyroid autoimmunity were higher in female SSc than in controls. Furthermore, three cases of GD in female SSc, and two cases of PTC were found in SSc patients *vs.* none in controls (12).

In a subsequent longitudinal study (47) the frequency of new cases of thyroid dysfunctions and autoimmunity were evaluated in 179 females SSc, *vs.* 179 matched control females, having a similar iodine intake. A higher incidence of new cases of thyroid dysfunction, as well as hypothyroidism, and thyroid autoimmunity were found in SSc compared to control subjects. New cases of hypothyroidism in SSc patients, were associated with a borderline high initial TSH level, AbTPO positivity, and a small and hypoechoic thyroid, as revealed by a logistic regression analysis. Since a high incidence of new cases of hypothyroidism or thyroid dysfunctions arose by this study, a thyroid function follow-up in female SSc was recommended (47).

In agreement, recently a study from New Zealand revealed a major prevalence of ATAs in SSc and SSc overlap syndrome in comparison to the general population (48).

Other two large studies evaluated >3000 patients with AT, or GD *vs*. age, and gender matched controls, showing an association between SSc and AT, or GD (27,28).

A study assessed the frequency of ATA and of the genetic association with HLA in SSc patients. The frequency of the HLA-DR15 allele was higher in subjects with AbTPO than in those without, this suggests that this allele may be a marker of immunogenicity for the production of AbTPO (42). On the basis of the abovementioned studies, most of the Authors suggested that for the clinical practice of SSc patients should be included an assessment of thyroid function, AbTPO and ultrasonography. Females, subjects reporting AbTPO+, and hypoechoic and small thyroid, may have thyroid function follow-up and proper treatment in due course (49, 50)

2.4 Rheumatoid arthritis

ATA was found in 11% of RA patients (43,51,52), with a wide variability ranging from 2%–32%. A study (53) reported high frequency of HT and ATA in these types of patients as well as in their families. Also, a major prevalence of RA in same-sexed siblings with thyroid autoimmune disorders *vs.* those without was reported (54).

A disagreement between the presence of ATA and thyroid function is still present. Subclinical hypothyroidism was observed with a wide variability; in a study only 2.8% of the RA patients were affected (55). However, another study found a three-fold increase of hypothyroidism and HT in RA women, in comparison with controls from the same region (51).

A major prevalence of AITD at diagnosis of RA and an increase of AITD incidence in the 5-year period previous RA diagnosis in comparison to the general population was observed in a Swedish study. Instead the risk to develop AITD is proposed to diminish below the expected rate after diagnosis of RA. The Authors, raised the question if AITD could have an influence on the pathogenesis of RA (or vice versa) and, conversely, the question if anti-rheumatic therapies may

prevent AITD (56).

More than 3.000 patients with AT, or GD were evaluated in two large studies (*vs.* age and gender matched controls) showing an aggregation between RA and AT, or GD (27,28).

A common genetic susceptibility was suggested by a study that, in patients with RA and HT, found a high prevalence of the HLA-A24, DR3 and DR4 antigens (57).

3. Cryoglobulinemia

Hepatitis C virus (HCV) infection plus AITD association was shown by different studies (58-62). Patients affected by chronic hepatitis C (CHC) exhibited high levels of AbTPO and an elevated risk of AT and hypothyroidism in females. The high frequency of AT in subjects affected by hepatitis C associated Mixed Cryoglobulinemia (MC+HCV), or CHC was confirmed by different studies (63-67).

A case-control study revealed a significantly more common frequency of serum AbTPO, and/or AbTg, and subclinical hypothyroidism in MC+HCV compared to HCV-negative controls (63). Furthermore, CHC and MC+HCV showed a higher prevalence of PTC, overall in presence of AT (64-66).

The hypothesis that HCV infection of thyrocytes could be implicated in CHC plus thyroid diseases association (68) was sustained by the detection of the virus in the thyroid of chronically infected subjects (69) and also by *in vitro* studies on human thyroid cell line (ML1) (68).

MC+HCV and AT association, has been recently showed in a large study (that used appropriate internal control groups), which prospectively evaluated 3069 patients with AT *vs.* age and gender matched controls (28).

Furthermore, in a large study that evaluated 3209 GD patients (*vs.* 1069 controls, 1069 AT and 1069 multinodular goiter patients; age and gender matched), has been shown a statistically

significant association between GD and HCV related MC, showing that GD is more frequent in these patients (27).

Thyroid disorders were observed in about 40% of CHC patients under an interferon (IFN)-α therapy, and thyroiditis can manifest as hypothyroidism or GD, or destructive thyroiditis. IFN-α can lead to thyroid AITD both via immune stimulatory, and as a direct toxic effect on the thyroid cells (70,71).

Recently, the prevalence of thyroid disorders was investigated in HCV patients under a sofosbuvir+ribavirin therapy, who were not treated previously with IFN. The Authors observed a major prevalence of thyroid dysfunctions in patients treated with IFN-α with respect to those treated with sofosbuvir (72).

4. Dermatologic autoimmune diseases

4.1 Vitiligo

VL is a hypo-pigmentary disorder of the skin with a complex pathophysiology, involving autoimmunity, and it is frequently aggregated with other autoimmune diseases. HT is the most common associated disease with a comorbidity up to 34% in VL (15). Also, in both adults and children with AITD, skin diseases were detected with similar prevalence, being VL the most common (73).

In line with the results of a recent study on 3209 GD patients [of whom 984 with Graves′ ophthalmopathy (GO)], 16.7% of them reported another associated autoimmune disease and the most commonly detected was VL (2.6%), followed by chronic autoimmune gastritis (2.4%) and other autoimmune disorders (27). Similarly, a high prevalence was observed in another large study in patients with AT (28).

Several susceptibility genes were determined in both VL and AITD, suggesting that the association observed between these two diseases may be partially explained by the sharing of subset of susceptibility genes. For example, single nucleotide polymorphism of the *PTPN22* gene, encoding a lymphoid-specific intracellular phosphatase is shared among these patients (74).

So, for these reasons, it can be useful to screen TSH values in patients affected by VL for thyroid dysfunctions (75).

4.2 Psoriasis and Psoriatic arthritis

PSO is a multifactorial inflammatory skin disorder involving immune system. About 2% of the European and North American population are affected by this disease (76).

PSO can also be associated with PsA, that is characterized by seronegative spondyloarthropathies, enthesitis and elevated C-reactive protein levels (77).

Consistently with the autoimmune nature of PSO, several other autoimmune diseases, including VL, alopecia and thyroiditis are associated with PSO (16,78). Autoimmunity in PSO is depicted by tumor necrosis factor (TNF)-α/IL-23/IL-17-shifted immune deviation. In AITD and PSO, there is a main role of T cells effectors, especially T helper 17 (Th17) (78).

In a first study a complete thyroid investigation was performed in 80 patients with PsA, in gender- and age-matched subjects (1:5) enrolled from general population (controls), and in 112 patients with RA with similar iodine intake. Women with PsA as well as those with RA, reported similar frequencies of AbTPO titer, hypoechoic thyroid, and subclinical hypothyroidism, that are more higher compared to controls (79).

The association between PsA and PSO and AT, has been recently showed in a large study with

appropriate internal control groups, that evaluated more than 3000 patients with AT, *vs.* age and gender matched controls (28).

In a cross-sectional study of 856 615 patients, 9615 received a diagnosis of PSO, and 1745 had HT. A significant aggregation existed for PSO and HT even after adjusting variables, such as gender, age, psoriatic arthropathy and the use of systemic anti-psoriatic agents that can be confounding factors (16).

However, a discrepant result was reported by Vassilatou et al. that investigated the prevalence of AT in psoriatic patients having or not PsA. They compared 114 psoriatic patients (30 with PsA) with 286 age and BMI matched subjects, not reporting PSO or known thyroid or autoimmune diseases, observing any difference in the prevalence of AT between psoriatic patients and controls (80).

New cases of thyroid disorders were investigated in 97 PsA and 97 matched controls, having a similar iodine intake (median follow-up of 74 months in PsA *vs.* 92 in controls). It was shown an increased rate of new cases of thyroid dysfunction, hypothyroidism, AbTPO+, and appearance of a small hypoechoic thyroid pattern in PsA, (especially in female), with respect to controls. A TSH in the normal range but at the higher limit, AbTPO+, and small thyroid volume are the risk factors for the development of thyroid dysfunction in female (81).

Another large study showed the association between PsA, and GD by examining 3209 patients with GD *vs.* age and gender matched controls (27).

These studies suggested that thyroid function follow-up and proper treatments should be performed regularly in female patients with a high risk, that report TSH in the normal range but at the higher limit, AbTPO+, hypoechoic and small thyroid (81).

5. Cytokines, chemokines, AITD and systemic autoimmune disorders

The important role covered by cytokines and chemokines in the AT and GD pathogenesis was demonstrated. Th1 lymphocytes, recruited into the thyroid tissue, may be the cause of a major IFN-γ and TNF-α production, that then stimulates the secretion of IFN-γ dependent chemokines CXCL10, CXCL9, CXCL11 from the thyroid cells (82,83); this allows the initiation and perpetuation of the autoimmune process.

The secretion of CXCL10, CXCL9, CXCL11 by cluster differentiation (CD)4+, CD8+, and natural killer is IFN-γ dependent; IFN-γ plus TNF-α, induce the secretion of these chemokines by thyrocytes and other target cells (84).

IFN-γ dependent chemokines by binding the CXC receptor 3 (CXCR3) (85), contribute to the pathogenesis of several autoimmune disorders, organ specific (e.g. GD, GO, T1D), or systemic (e.g. MC, SS, SLE, sarcoidosis, PSO or SSc) (12,86-92).

The IFN-γ dependent chemokines secreted by the inflamed tissue of the target organs of the autoimmune process enter into the circulation. In fact, circulating levels of CXCL10, CXCL9 and CXCL11 are high in subjects with AT, GD and GO.

High levels of circulating CXCL10, CXCL9 and CXCL11, were observed in hypothyroid with AT, especially if a thyroid hypoechoic ultrasonographic pattern is present, that indicates a more severe lympho-monocytic infiltration (84,93).

These findings, may lead to hypothesize that CXCL10 may be a marker of a more aggressive and strong inflammatory response in the thyroid, followed by thyroid destruction and hypothyroidism.

In patients with GO a significant reduction of circulating CXCL10, CXCL9 occurs during corticosteroids and/or radiotherapy treatments, this finding suggests that these chemokines could aid by serving as guidelines in therapeutic decision-making in patients with GO (94,95).

Therefore, the detection of high level of CXCL10, CXCL9 in peripheral fluids is a marker of a Th1 orientated-immune response (85). However, more investigations are needed to evaluate whether IFN-γ dependent chemokines are new therapeutic targets in HT, GD and GO (96,97).

IFN-γ dependent chemokines serum and tissue expressions are increased in systemic rheumatologic or dermatologic disorders; this underlined the importance of a shared immune-pathogenesis of these pathologies, in which is mainly present a predominant autoimmune response Th1-related in the initial, and/or in their active phases (86,98,99).

Conclusion

HT, GD, ATA and thyroid function abnormalities were commonly observed in patients with systemic rheumatologic autoimmune diseases, such as SS, RA, SLE, SSc, and cryoglobulinemia, and in patients with dermatologic autoimmune diseases, such as VL, PSO and also PsA. Although the pathogenic mechanism of this association is unknown, several studies focused on the importance of a shared genetic susceptibility in patients with AITD and systemic autoimmunity. Environmental factors could be also involved in the aggregation of autoimmune diseases.

Moreover, since a Th1 prevalent autoimmune response is a characteristic of the organ specific autoimmune diseases, (e.g. AT, GD), and/or of the systemic rheumatologic disorders, or dermatologic autoimmune disorders in their initial, and active phases, with an increased CXCL10 serum and/or tissue expressions, this underlined the importance of a common immune-pathogenesis of these diseases. The complex interaction among genetics and environmental modifications that affect gene expression, immune system response and, finally, the pathogenesis of autoimmune diseases could be on the basis of the coexistence of autoimmune diseases.

Thyroid dysfunctions may have an important clinical impact, thus it is suggested to perform a periodical evaluation of the thyroid function in women with systemic or dermatologic autoimmunity, overall if thyroid autoantibodies are present.

Conflict of Interest

The Authors have nothing to declare.

Role of the funding source

The Authors have nothing to declare.

Summary

The aggregation between AITD with rheumatologic, or dermatologic autoimmune diseases has been described by different studies. The pathogenic mechanism of this association is unknown, however a shared genetic susceptibility and environmental factors have been suggested. The complex interaction among genetics and environment modifications that affect gene expression, and immune system response are also at the basis of pathogenesis of autoimmune diseases and their association. Moreover, a common immune-pathogenesis of these diseases is underlined by a Th1 prevalent autoimmune response that is a characteristic of the organ specific autoimmune diseases, (e.g. AT, GD), and/or of the systemic rheumatologic or dermatologic autoimmune disorders in their initial, and active phases, with an increased CXCL10 serum and/or tissue expressions. Thyroid dysfunctions may have an important clinical impact, thus it is suggested to perform a periodical evaluation of the thyroid function in women with systemic or dermatologic autoimmunity, overall if thyroid autoantibodies are present.

Practice Points

- Association between AITD with rheumatologic, or dermatologic autoimmune diseases are present in about 20% of patients.

- Patients with rheumatologic or dermatologic autoimmune diseases, overall if females and with circulating thyroid autoantibodies, need to be periodically evaluated for thyroid dysfunctions.

- Coexistence of autoimmune diseases is due to the complex interaction among genetics and environment modifications that affect gene expression, immune system response and subsequently the pathogenesis of autoimmune diseases; risk factors should be identified to evaluate patients at high risk of AITD.

Research Agenda

- Large prospective longitudinal studies in patients with AITD need to be done to evaluate a precise incidence of rheumatologic or dermatologic autoimmune diseases.

- Genetic susceptibility studies should be performed in patients with the association of AITD with rheumatologic or dermatologic autoimmune disorders.

- Environmental risk factors need to be studied in patients with the association of AITD with rheumatologic or dermatologic autoimmune disorders.

- The Th1 prevalent autoimmune response is a characteristic of the organ specific autoimmune diseases, and/or of the systemic rheumatologic or dermatologic autoimmune disorders in their initial, and active phases, with an increased CXCL10 serum and/or tissue

expressions. Drugs targeting the Th1 immune response might be evaluated in patients with AITD to prevent the appearance of other autoimmune disorders.

References

1. Orgiazzi J. Thyroid autoimmunity. *La Presse Médicale* 2012;**41**: e611-e625.
2. Vanderpump MP, Tunbridge WM, French JM, et al. The incidence of thyroid disorders in the community: a twenty-year follow-up of the Whickham Survey. *Clinical endocrinology (Oxford)* 1995;**43**: 55-68.
3. McLeod DS, Cooper DS. The incidence and prevalence of thyroid autoimmunity. *Endocrine* 2012;**42**: 252-265.
4. Pedersen IB, Laurberg P, Knudsen N, et al. An increased incidence of overt hypothyroidism after iodine fortification of salt in Denmark: a prospective population study, *The Journal of Clinical Endocrinology and Metabolism* 2007;**92**: 3122-3127.
5. Taylor PN, Albrecht D, Scholz A, et al. Global epidemiology of hyperthyroidism and hypothyroidism. *Nature reviews. Endocrinology* 2018;**14**: 301-316.
6. Latina A, Gullo D, Trimarchi F, Benvenga S. Hashimoto's thyroiditis: similar and dissimilar characteristics in neighboring areas. Possible implications for the epidemiology of thyroid cancer. *PloS One* 2013;**8**: e55450.
7. Rizzo M, Sindoni A, Talamo Rossi R, et al. Annual increase in the frequency of papillary thyroid carcinoma as diagnosed by fine-needle aspiration at a cytology unit in Sicily. *Hormones (Athens, Greece)* 2013;**12**: 46-57.
8. Dittmar M, Kahaly GJ. Polyglandular autoimmune syndromes: immunogenetics and long-term follow-up. *The Journal of clinical endocrinology and metabolism* 2003;**88**: 2983-2992.
9. Antonelli A, Tuomi T, Nannipieri M, et al. Autoimmunity to CD38 and GAD in Type I and Type II diabetes: CD38 and HLA genotypes and clinical phenotypes. *Diabetologia* 2002;**45**: 1298-1306
10. Aversa T, Corica D, Zirilli G, et al. Phenotypic Expression of Autoimmunity in Children With Autoimmune Thyroid Disorders. *Frontiers in endocrinology* 2019;**10**: 476.

11. Ruggeri RM, Trimarchi F, Giuffrida G, et al. Autoimmune comorbidities in Hashimoto's thyroiditis: different patterns of association in adulthood and childhood/adolescence. *European journal of endocrinology* 2017;**176**:133-141.
12. Antonelli A, Ferri C, Fallahi P, et at. Clinical and subclinical autoimmune thyroid disorders in systemic sclerosis. *European journal of endocrinology* 2007;**156**:431-437.
13. Antonelli A, Fallahi P, Mosca M, Ferrari SM, Ruffilli I, Corti A, Panicucci E, Neri R, Bombardieri S. Prevalence of thyroid dysfunctions in systemic lupus erythematosus. *Metabolism: clinical and experimental* 2010;**59**: 896-900. *
14. Antonelli A, Mosca M, Fallahi P, et al. Thyroid cancer in systemic lupus erythematosus: a case-control study. *The Journal of clinical endocrinology and metabolism* 2010;**95**: 314-318.
15. Vachiramon V, Harnchoowong S, Onprasert W, Chanprapaph K. Prevalence of thyroid abnormalities in thai patients with vitiligo. *BioMed research international* 2017;**2017**: 7502935.
16. Kiguradze T, Bruins FM, Guido N, et al. Evidence for the association of Hashimoto's thyroiditis with psoriasis: a cross-sectional retrospective study. *International journal of dermatology* 2017;**56**: 553-556.
17. Anaya JM, Restrepo-Jiménez P, Rodríguez Y, et al. Sjögren's Syndrome and Autoimmune Thyroid Disease: Two Sides of the Same Coin. *Clinical reviews in allergy & immunology* 2019;**56**: 362-374.
18. Alfaris N, Curiel R, Tabbara S, Irwig MS. Autoimmune thyroid disease and Sjögren syndrome. *Journal of Clinical Rheumatology* 2010;**16**: 146-147.
19. Amador-Patarroyo MJ, Arbelaez JG, Mantilla RD, et al. Sjögren's syndrome at the crossroad of polyautoimmunity. *Journal of autoimmunity* 2012;**39**: 199-205.
20. Ruggeri RM, Galletti M, Mandolfino MG, et al. Thyroid hormone autoantibodies in primary Sjögren syndrome and rheumatoid arthritis are more prevalent than in autoimmune thyroid

disease, becoming progressively more frequent in these diseases. *Journal of Endocrinological Investigation* 2002;**25**: 447-454.

21. D'Arbonneau F, Ansart S, Le Berre R, et al. Thyroid dysfunction in primary Sjögren's syndrome: a long-term followup study. *Arthritis and Rheumatism* 2003;**49**: 804-809. *
22. Abrol E, González-Pulido C, Praena-Fernández JM, Isenberg DA. A retrospective study of long-term outcomes in 152 patients with primary Sjogren's syndrome: 25-year experience. *Clinical medicine : journal of the Royal College of Physicians of London* 2014;**14**:157-164.
23. Robazzi TC, Adan LF. Autoimmune thyroid disease in patients with rheumatic diseases. *Revista brasileira de reumatologia* 2012;**52**: 417-430.
24. Lazarus MN, Isenberg DA. Development of additional autoimmune diseases in a population of patients with primary Sjögren's syndrome. *Annals of the rheumatic diseases* 2005;**64**: 1062-1064.
25. Zeher M, Horvath IF, Szanto A, Szodoray P. Autoimmune thyroid diseases in a large group of Hungarian patients with primary Sjögren's syndrome. *Thyroid* 2009;**19**:39-45.
26. Lu MC, Yin WY, Tsai TY, et al. Increased risk of primary Sjögren's syndrome in female patients with thyroid disorders: a longitudinal population-based study in Taiwan. *PloS One* 2013;**8**: e77210.
27. Ferrari SM, Fallahi P, Ruffilli I, et al. The association of other autoimmune diseases in patients with Graves' disease (with or without ophthalmopathy): Review of the literature and report of a large series. *Autoimmunity reviews* 2019;**18**:287-292. *
28. Fallahi P, Ferrari SM, Ruffilli I, et al. The association of other autoimmune diseases in patients with autoimmune thyroiditis: Review of the literature and report of a large series of patients. *Autoimmunity reviews* 2016;**15**:1125-1128. *
29. Griffiths B, Mosca M, Gordon C. Assessment of patients with systemic lupus erythematosus and the use of lupus disease activity indices. *Best practice & research. Clinical rheumatology* 2005;**19**: 685-708.

30. Pyne D, Isenberg DA. Autoimmune thyroid disease in systemic lupus erythematosus. *Annals of the rheumatic diseases* 2002;**61**: 70-72.

31. Biró E, Szekanecz Z, Czirják L, et al. Association of systemic and thyroid autoimmune diseases. *Clinical rheumatology* 2006;**25**: 240-245.

32. Appenzeller S, Pallone AT, Natalin RA, Costallat LT. Prevalence of thyroid dysfunction in systemic lupus erythematosus. *Journal of Clinical Rheumatology* 2009;**15**: 117-119.

33. Vianna JL, Haga HJ, Asherson RA, et al. A prospective evaluation of antithyroid antibody prevalence in 100 patients with systemic lupus erythematosus. *The Journal of Rheumatology* 1991;**18**: 1193-1195.

34. Blich M, Rozin A, Edoute Y. Systemic lupus erythematosus and thyroid disease. *The Israel Medical Association Journal:IMAJ* 2004;**6**: 218-220.

35. Lin WY, Chang CL, Fu LS, et al. Systemic lupus erythematosus and thyroid disease: A 10-year study. *Journal of microbiology, immunology, and infection* 2015;**48**: 676-683.

36. Wei S, Yang Z, Xie S, et al. Autoimmune Thyroid Disease in Patients with Systemic Lupus Erythematosus: A 7-year Retrospective Study in China. *The American journal of the medical sciences* 2018;**356**: 344-349.

37. Namjou B, Kelly JA, Kilpatrick J, et al. Linkage at 5q14.3-15 in multiplex systemic lupus erythematosus pedigrees stratified by autoimmune thyroid disease. *Arthritis and Rheumatism* 2005;**52**: 3646-3650.

38. Scherbaum, W. Pathogenesis of Autoimmune Thyroiditis. *Nuklearmediziner* 1993;**16**: 241-249.

39. Ferri C, Valentini G, Cozzi F, et al. Systemic sclerosis: demographic, clinical, and serologic features and survival in 1,012 Italian patients. *Medicine* 2002;**81**: 139-153.

40. Gordon MB, Klein I, Dekker A, et al. Thyroid disease in progressive systemic sclerosis: increased frequency of glandular fibrosis and hypothyroidism. *Annals of Internal Medicine* 1981;**95**:431-435.

41. Kahl LE, Medsger TA Jr, Klein I. Prospective evaluation of thyroid function in patients with systemic sclerosis (scleroderma). *The Journal of Rheumatology* 1986;**13**: 103-107.
42. Molteni M, Barili M, Eisera N, et al. Anti-thyroid antibodies in Italian scleroderma patients: association of anti-thyroid peroxidase (anti-TPO) antibodies with HLA-DR15. *Clinical and Experimental Rheumatology* 1997;**15**: 529-534.
43. Innocencio RM, Romaldini JH, Ward LS. Thyroid autoantibodies in autoimmune diseases. *Medicina (B Aires)* 2004;**64**: 227-230.
44. Shoaleh-var M, Momtaz AH, Jamshidi C. Scleroderma and hyperthyroidism. Report of a case. *JAMA* 1976;**235**: 752-753.
45. Nicholson D, White S, Lipson A, et al. Progressive systemic sclerosis and Graves' disease. Report of three cases. *Archives of Internal Medicine* 1986;**146**: 2350-2352.
46. Avouac J, Airò P, Dieude P, et al. Associated autoimmune diseases in systemic sclerosis define a subset of patients with milder disease: results from 2 large cohorts of European Caucasian patients. *The Journal of Rheumatology* 2010;**37**: 608-614.
47. Antonelli A, Fallahi P, Ferrari SM, et al. Incidence of thyroid disorders in systemic sclerosis: results from a longitudinal follow-up. *The Journal of Clinical Endocrinology and Metabolism* 2013;**98**: E1198-E1202.
48. Solanki KK, Al-Majmuei M, White DHN. High Prevalence of Antithyroid Antibodies in a New Zealand Cohort of Patients With Systemic Sclerosis. *Journal of clinical rheumatology : practical reports on rheumatic & musculoskeletal diseases* 2018;**24**: 264-271.
49. Fallahi P, Ruffilli I, Giuggioli D, et al. Association between Systemic Sclerosis and Thyroid Diseases. *Frontiers in Endocrinology* 2017;**8**: 266.
50. Giuggioli D, Lumetti F, Colaci M, et al. Rituximab in the treatment of patients with systemic sclerosis. Our experience and review of the literature. *Autoimmunity reviews.* 2015;**14**: 1072-1078.

51. Shiroky JB, Cohen M, Ballachey ML, Neville C. Thyroid dysfunction in rheumatoid arthritis: a controlled prospective survey. *Annals of the Rheumatic Diseases* 1993;**52**: 454-456.

52. Tektonidou MG, Anapliotou M, Vlachoyiannopoulos P, Moutsopoulos HM. Presence of systemic autoimmune disorders in patients with autoimmune thyroid diseases. *Annals of the Rheumatic Diseases* 2004;**63**: 1159-1161.

53. Silman AJ, Ollier WE, Bubel MA. Autoimmune thyroid disease and thyroid autoantibodies in rheumatoid arthritis patients and their families. *British Journal of Rheumatology* 1989;**28**: 18-21.

54. Deighton CM, Fay A, Walker DJ. Rheumatoid arthritis in thyroid disease positive and negative same-sexed sibships. *British Journal of Rheumatology* 1992;**31**: 13-17.

55. Atzeni F, Doria A, Ghirardello A, et al. Anti-thyroid antibodies and thyroid dysfunction in rheumatoid arthritis: prevalence and clinical value. *Autoimmunity* 2008;**41**: 111-115.

56. Waldenlind K, Saevarsdottir S, Bengtsson C, Askling. Risk of Thyroxine-Treated Autoimmune Thyroid Disease Associated With Disease Onset in Patients With Rheumatoid Arthritis. *JAMA network open*. 2018;**1**: e183567. *

57. Punzi L, Schiavon F, Ramonda R, et al. Anti-thyroid microsomal antibody in synovial fluid as a revealing feature of seronegative autoimmune thyroiditis. *Clinical Rheumatology* 1991;**10**: 181-183.

58. Antonelli A, Ferri C, Fallahi P, et al. Thyroid disorders in chronic hepatitis C virus infection. *Thyroid* 2006;**16**: 563-572.

59. Indolfi G, Stagi S, Bartolini E, et al. Thyroid function and anti-thyroid autoantibodies in untreated children with vertically acquired chronic hepatitis C virus infection. *Clinical Endocrinology (Oxford)* 2008;**68**: 117-121.

60. Antonelli A, Ferri C, Pampana A, et al. Thyroid disorders in chronic hepatitis. *The American journal of medicine* 2004;**117**: 10-3.

61. Ferri C, Sebastiani M, Giuggioli D, et al. Hepatitis C virus syndrome: A constellation of organ- and non-organ specific autoimmune disorders, B-cell non-Hodgkin's lymphoma, and cancer. *World journal of hepatology* 2015;**7**: 327-343.

62. Zignego AL, Gragnani L, Piluso A, et al. Virus-driven autoimmunity and lymphoproliferation: the example of HCV infection. *Expert review of clinical immunology* 2015;**11**: 15-31.

63. Antonelli A, Ferri C, Fallahi P, et al. Thyroid involvement in patients with overt HCV-related mixed cryoglobulinaemia. *QJM* 2004;**97**: 499-506.

64. Antonelli A, Ferri C, Fallahi P, et al. Thyroid cancer in HCV-related chronic hepatitis patients: a case-control study. *Thyroid* 2007;**17**: 447-451.

65. Ferri C, Antonelli A, Mascia MT, et al. B-cells and mixed cryoglobulinemia. *Autoimmunity Reviews* 2007;**7**: 114-120.

66. Antonelli A, Ferri C, Fallahi P, et al. Thyroid cancer in HCV-related mixed cryoglobulinemia patients. *Clinical and Experimental Rheumatology* 2002;**20**: 693-696.

67. Fallahi P, Ferrari SM, Giuggioli D, et al. Thyroid involvement in hepatitis C - associated mixed cryoglobulinemia. *Hormones: international journal of endocrinology and metabolism* 2014;**13**: 16-23.

68. Blackard JT, Kong L, Huber AK, Tomer Y. Hepatitis C virus infection of a thyroid cell line: implications for pathogenesis of hepatitis C virus and thyroiditis. *Thyroid* 2013;**23**: 863-870.

69. Bartolomé J, Rodríguez-Iñigo E, Quadros P, et al. Detection of hepatitis C virus in thyroid tissue from patients with chronic HCV infection. *Journal of Medical Virology* 2008;**80**: 1588-1594.

70. Menconi F, Hasham A, Tomer Y. Environmental triggers of thyroiditis: hepatitis C and interferon-α. *Journal of Endocrinological Investigation* 2011;**34**: 78-84. *

71. Ferri C, Antonelli A, Mascia MT, et al. HCV-related autoimmune and neoplastic disorders: the HCV syndrome. *Digestive and Liver Disease: Official Journal of the Italian Society of*

Gastroenterology and the Italian Association for the Study of the Liver 2007;**39Suppl1**: S13-S21.

72. Wahid B, Waqar M, Rasool N, et al. Prevalence of thyroid stimulating hormone dysfunction among sofosbuvir-treated HCV-infected patients: A real-world clinical experience. *Journal of medical virology* 2019;**91**: 514-517.
73. Ruggeri RM, Trimarchi F, Giuffrida G, et al. Autoimmune comorbidities in Hashimoto's thyroiditis: different patterns of association in adulthood and childhood/adolescence. *European journal of endocrinology* 2017;**176**: 133-141. *
74. Czajkowski R, Męcińska-Jundziłł K. Current aspects of vitiligo genetics. *Postępy dermatologii i alergologii* 2014;**31**: 247-255.
75. Liu M, Murphy E, Amerson EH. Rethinking screening for thyroid autoimmunity in vitiligo. *Journal of the American Academy of Dermatology* 2016;**75**: 1278-1280.
76. Boehncke WH, Schon MP. Psoriasis. *Lancet* 2015;**386**: 983-994.
77. Takata T, Takahashi A, Taniguchi Yet al. Detection of asymptomatic enthesitis in psoriasis patients: an onset of psoriatic arthritis?. *The Journal of dermatology* 2016;**43**: 650-654.
78. Furue K, Ito T, Tsuji G, et al. Autoimmunity and autoimmune co-morbidities in psoriasis. *Immunology* 2018;**154**: 21-27.
79. Antonelli A, Delle Sedie A, Fallahi P,et al. High prevalence of thyroid autoimmunity and hypothyroidism in patients with psoriatic arthritis. *The Journal of rheumatology* 2006;**33**: 2026-2028.
80. Vassilatou E, Papadavid E, Papastamatakis P, et al. No association of psoriasis with autoimmune thyroiditis. *Journal of the European Academy of Dermatology and Venereology:JEADV* 2017;**31**: 102-106.
81. Fallahi P, Ferrari SM, Ruffilli I, et al. Increased incidence of autoimmune thyroid disorders in patients with psoriatic arthritis: a longitudinal follow-up study. *Immunologic research* 2017;**65**: 681-686. *

82. Antonelli A, Ferrari SM, Fallahi P, et al. Interferon-alpha, -beta and -gamma induce CXCL9 and CXCL10 secretion by human thyrocytes: modulation by peroxisome proliferator-activated receptor-gamma agonists. *Cytokine* 2010;**50**: 260-267.

83. Antonelli A, Ferrari SM, Fallahi P, et al. Monokine induced by interferon gamma (IFNgamma) (CXCL9) and IFNgamma inducible T-cell alpha-chemoattractant (CXCL11) involvement in Graves' disease and ophthalmopathy: modulation by peroxisome proliferator-activated receptor-gamma agonists. *The Journal of clinical endocrinology and metabolism* 2009;**94**: 1803-1809.

84. Ruffilli I, Ferrari SM, Colaci M, et al. IP-10 in autoimmune thyroiditis. *Hormone and metabolic research* 2014;**46**: 597-602.

85. Antonelli A, Rotondi M, Fallahi P, et al. Increase of CXC chemokine CXCL10 and CC chemokine CCL2 serum levels in normal ageing. *Cytokine* 2006;**34**:32-38.

86. Antonelli A, Ferrari SM, Giuggioli D, et al. Chemokine (C-X-C motif) ligand (CXCL)10 in autoimmune diseases. *Autoimmunity Reviews* 2014;**13**: 272-280. *

87. Antonelli A, Baj G, Marchetti P, et al. Human anti-CD38 autoantibodies raise intracellular calcium and stimulate insulin release in human pancreatic islets. *Diabetes* 2001;**50**: 985-991.

88. Antonelli A, Fallahi P, Delle Sedie A, et al. High values of Th1 (CXCL10) and Th2 (CCL2) chemokines in patients with psoriatic arthtritis. *Clinical and Experimental Rheumatology* 2009;**27**: 22-27.

89. Antonelli A, Ferri C, Fallahi P, et al. High values of CXCL10 serum levels in mixed cryoglobulinemia associated with hepatitis C infection. *The American journal of gastroenterology* 2008;**103**: 2488-2494. *

90. Antonelli A, Ferri C, Fallahi P, et al. Th1 and Th2 chemokine serum levels in systemic sclerosis in the presence or absence of autoimmune thyroiditis. *The Journal of rheumatology* 2008;**35**: 1809-1811.

91. Fallahi P, Ferri C, Ferrari SM, et al. Cytokines and HCV-related disorders. *Clinical & developmental immunology* 2012;**2012**: 468107.

92. Antonelli A, Fazzi P, Fallahi P, et al. Prevalence of hypothyroidism and Graves disease in sarcoidosis. *Chest* 2006;**130**: 526-532.

93. Antonelli A, Ferrari SM, Frascerra S, et al. Circulating chemokine (CXC motif) ligand (CXCL)9 is increased in aggressive chronic autoimmune thyroiditis, in association with CXCL10. *Cytokine* 2011;**55**: 288-293.

94. Zhu W, Ye L, Shen L, et al. A prospective, randomized trial of intravenous glucocorticoids therapy with different protocols for patients with graves' ophthalmopathy. *The Journal of clinical endocrinology and metabolism* 2014;**99**: 1999-2007.

95. Mysliwiec J, Palyga I, Kosciuszko M, et al. Circulating CXCL9 and CXCL10 as markers of activity of Graves' orbitopathy during treatment with corticosteroids and teleradiotherapy. *Hormone and metabolic research* 2012;**44**: 957-961.

96. Fallahi P, Ferrari SM, Corrado A, et al. Targeting Chemochine (C-X-C motif) Receptor 3 in Thyroid Autoimmunity. *Recent patents on endocrine, metabolic, and immune drug discovery* 2014;**8**: 95-101.

97. Lee SH, Lim SY, Choi JH, et al. Benzylideneacetophenone derivatives attenuate IFN-γ-induced IP-10/CXCL10 production in orbital fibroblasts of patients with thyroid-associated ophthalmopathy through STAT-1 inhibition. *Experimental & molecular medicine* 2014;**46**: 100.

98. Lee EY, Lee ZH, Song YW. CXCL10 and autoimmune diseases. *Autoimmunity reviews* 2009;**8**: 379-383.

99. Antonelli A, Ferrari SM, Corrado A, et al. CXCR3, CXCL10 and type 1 diabetes. *Cytokine and growth factor reviews* 2014;**25**: 57-65.