THE ASSOCIATION OF OTHER AUTOIMMUNE DISEASES IN PATIENTS WITH THYROID AUTOIMMUNITY

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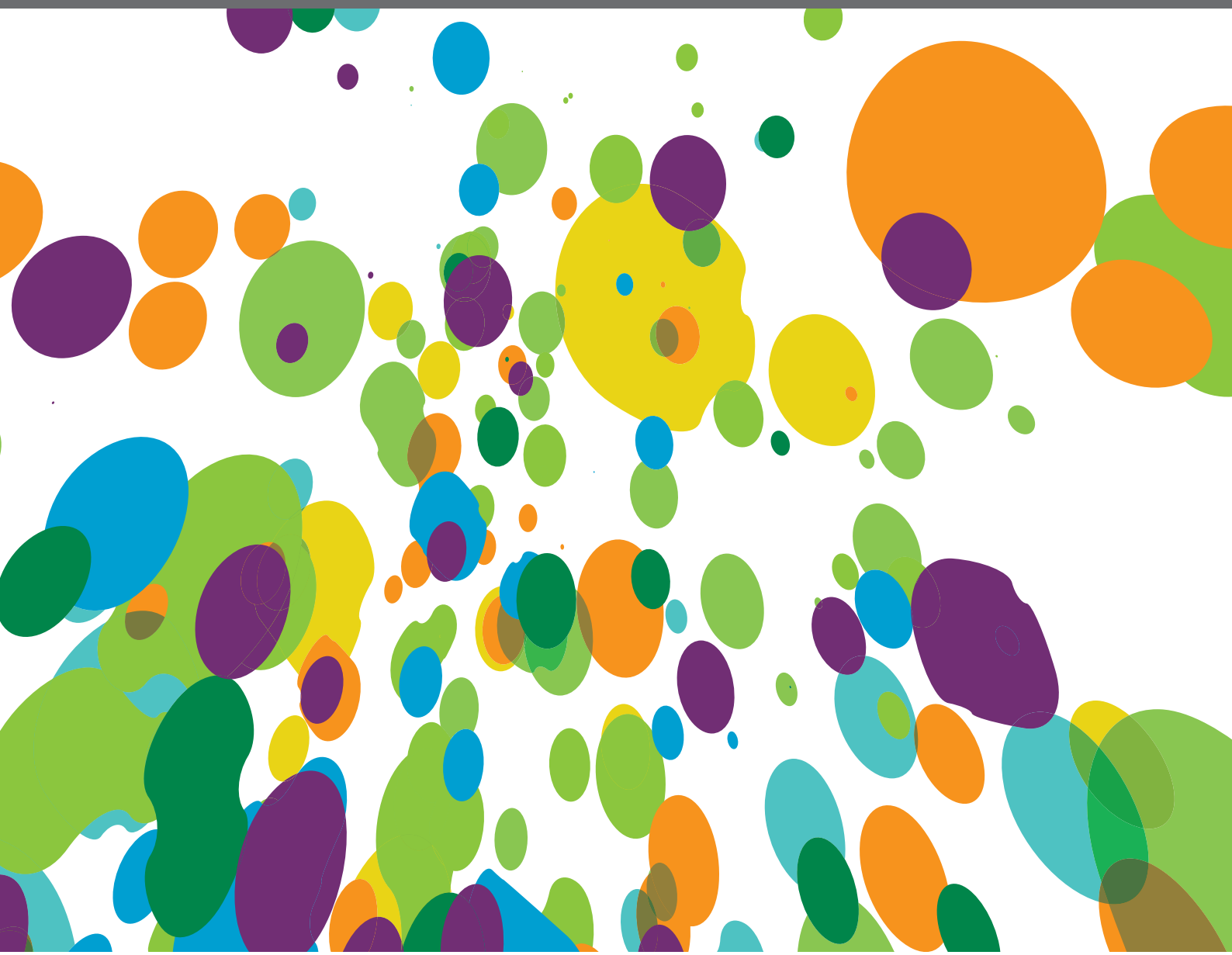

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THE ASSOCIATION OF OTHER AUTOIMMUNE DISEASES IN PATIENTS WITH THYROID AUTOIMMUNITY

Topic Editors:
Alessandro Antonelli, University of Pisa, Italy
Salvatore Benvenga, University of Messina, A.O.U. Policlinico Gaetano Martino, Italy

Autoimmune thyroid diseases (AITD) are T cell-mediated organ-specific autoimmune disorders resulting from an immune dysregulation leading to a thyroid immune attack (Antonelli and Benvenga). Graves' disease and Hashimoto's thyroiditis are the two main clinical presentations of AITD, and their clinical hallmarks are thyrotoxicosis and hypothyroidism, respectively.

In many cases, AITD may be associated in the same patient with other organ-specific autoimmune attacks (such as in the case of type II autoimmune polyglandular syndrome, or type I diabetes, etc). Furthermore, AITD and thyroid function abnormalities have been frequently described in patients with systemic rheumatologic autoimmune diseases. Conversely, patients affected with the above mentioned autoimmune disorders are more frequently affected by AITD.

In this Research Topic, constituted by nineteen papers, we review and discuss new evidence about the association of other autoimmune diseases in patients with AITD. Among other organ-specific autoimmune disorders, the associations of AITD with chronic autoimmune gastritis (Cellini et al.), vitiligo (Baldini E et al.), lichen (Guarneri et al.), psoriasis (Ruffilli et al.), myasthenia gravis (Lopomo and Berrih-Aknin) and glomerulopathies (Santoro et al.) have been treated. Also the associations of AITD, in systemic autoimmune diseases have been treated (as Sjögren's syndrome, Baldini C et al.; systemic sclerosis, Fallahi et al.; systemic lupus erythematosus, Ferrari et al.; Antiphospholipid syndrome, Versini; sarcoidosis, Fazzi et al.; the autoimmune/inflammatory syndrome induced by adjuvants, Watad et al.; rheumatoid arthritis, Bliddal et al.; Hepatitis C Virus and mixed cryoglobulinemia, Ferri et al.; and, psoriathic arthritis, Ruffilli et al.). Furthermore peculiar aspects associated with post partum thyroiditis have been reviewed too (Di Bari et al., Le Donne et al.).

The exact pathogenetic mechanisms underlying the above reported associations are not completely known. It has been hypothesized that the influence of genetic (Coppedè), and environmental factors (Antonelli and Benvenga), could lead to the onset of autoimmune phenomena in different organs in the same subject, characterized by predominance of a Th1 immune pattern at the beginning, and in the active phase of these disorders.

In conclusion, an association of other autoimmune diseases in patients with thyroid autoimmunity has been shown, and this Research Topic provides an extensive update of the literature, and suggests interesting points for new investigations.

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Table of Contents

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EDITORIAL
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Editorial: The Association of Other Autoimmune Diseases in Patients With Thyroid Autoimmunity

Alessandro Antonelli[1]* *and Salvatore Benvenga*[2,3,4]

[1] Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy, [2] Department of Clinical and Experimental Medicine, Section of Endocrinology, University of Messina, Messina, Italy, [3] Master Program on Childhood, Adolescent and Women's Endocrine Health, University of Messina, Messina, Italy, [4] Interdepartmental Program on Molecular & Clinical Endocrinology, and Women's Endocrine Health, University Hospital, A.O.U. Policlinico Gaetano Martino, Messina, Italy

Keywords: autoimmune thyroid diseases, rheumatological autoimmune disorders, Graves' disease, Hashimoto's thyroiditis, thyroid autoantibodies, postpartum, epigenetics, environmental factors

Editorial on the Research Topic

The Association of Other Autoimmune Diseases in Patients With Thyroid Autoimmunity

Autoimmune thyroid diseases (AITD) derive from a dysregulation of the immune system causing an immune attack on the thyroid, and involve two main clinical presentations: Graves' disease (GD) and Hashimoto's thyroiditis (AT) (1).

Recently, a significant increase of the prevalence of other autoimmune disorders in AT patients has been shown (by a large prospective, case-control, study) for the following diseases: vitiligo (Vit), chronic autoimmune gastritis (CAG), sjogren disease (SS), rheumatoid arthritis (RA), multiple sclerosis, polymyalgia rheumatica (Polym), celiac disease, diabetes, systemic lupus erythematosus (SLE), sarcoidosis (S), alopecia, psoriathic arthritis (PsA), systemic sclerosis (SSc), and hepatitis C virus (HCV)-related mixed cryoglobulinemia (MC); and a near significant prevalence has also been shown for Addison's disease and ulcerative colitis (2). Furthermore, the association of three autoimmune disorders was observed in AT patients (the most frequent associations were AT + CAG + Vit and AT + CAG + Polym) (2).

Moreover, in a large number ($n = 2{,}791$) of UK patients with GD a significant association with RA, pernicious anemia, SLE, Addison's disease, celiac disease, and Vit has been shown. A relative "clustering" of AITD in the index case with parental AITD was present. Furthermore relative risks for most other coexisting autoimmune disorders were strongly increased among parents of index cases (3).

Conversely, patients affected with the above mentioned autoimmune disorders are more frequently affected by AITD (1).

In this Research Topic, constituted by eighteen papers, we review and discuss new evidence about the association of other autoimmune diseases in patients with AITD, providing a stimulating overview of the present knowledge.

The paper by Coppedè discusses the increasing evidence about the importance of epigenetic modifications (such as changes in DNA methylation, non-coding RNA molecules-mediated gene silencing, and covalent modifications of histone tails) in the pathogenesis of AITD, as a possible result of environmental injuries that trigger these disorders.

The autoimmune/inflammatory syndrome induced by adjuvants (ASIA), presented by Shoenfeld and Agmon-Levin (4), is constituted by different autoimmune conditions induced by the exposure to various adjuvants, that are present in many vaccines, and induce immune reactions (5). The review by Watad et al. summarizes the current knowledge on ASIA syndrome presented as endocrinopathies, concentrating on adjuvants-associated AITD.

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Edited and reviewed by:
Rauf Latif,
Icahn School of Medicine at Mount Sinai, United States

***Correspondence:**
Alessandro Antonelli
alessandro.antonelli@med.unipi.it

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Fallahi et al. provide evidence on the association of SSc and thyroid disorders. The majority of the reviewed papers report an association among SSc, hypothyroidism, and AT (and few cases of GD). Moreover, a high prevalence of thyroid cancer, in SSc patients with AT, has been observed.

Increased incidence of AT and hypothyroidism has been shown in SLE patients, particularly in females. The review by Ferrari et al. suggests female patients with SLE, showing a high risk profile of AITD [a small and hypoechoic thyroid, a thyroid-stimulating hormone (TSH) in the upper quartile of the normal range, and antithyroid peroxidase antibodies (AbTPO) positivity], should be periodically re-evaluated for thyroid dysfunction, and when necessary due treatments.

Mixed cryoglobulinemia is the most important systemic HCV-related extrahepatic disease (6). HCV is a hepato- and lymphotropic virus responsible for many autoimmune/lymphoproliferative and/or neoplastic disorders and a high incidence of new cases of AT and thyroid dysfunctions have been reported in MC patients (6). The paper by Ferri et al. describes the prevalence and the clinical and serological features associated with thyroid involvement, in particular AT and papillary thyroid cancer, in patients affected by chronic HCV infection in presence/absence of cryoglobulinemic vasculitis.

Regarding RA, many studies have reported that the therapy with biological antirheumatic agents (BAAs) are able to modify the inflammatory response both in RA such as in AITD. The paper by Bliddal et al. investigates how the use of such agents affect the thyroid function and autoimmunity in RA patients.

Psoriasis (PsO) is a chronic autoimmune skin disease, and PsA (a chronic inflammatory arthritis) is present in about 30% of patients with PsO. An increased rate of new cases of patients with positive AbTPO, hypothyroidism, thyroid dysfunctions and appearance of a small thyroid with signs of hypoechogenicity, overall in females, has been reported in PsA (7). PsO, PsA, and their association with AITD have been evaluated by Ruffilli et al. suggesting that a thyroid screening should be done routinely in PsA female patients with an elevated risk pattern (a TSH level in the upper quartile of the reference range, AbTPO positivity, a small and hypoechogenic thyroid).

Also the association of S and thyroid autoimmunity has been shown by different studies in a wide range of variability, particularly in the female gender (8). Fazzi et al. provide evidence about the possible association between S and thyroid autoimmunity.

Sjögren's syndrome and AITD frequently coexist in clinical practice, leading to a complex overlapping disorder that represents a particular example of the expression of heterogeneity in patients with autoimmune disorders. Baldini et al. provide a critical overview of the recent literature on the pathogenesis and clinical features of SS-AITD overlapping disease.

Non-segmental Vit is an autoimmune disorder arising from an autoimmune response against melanocytes in the skin, and it is often associated with other autoimmune disorders (9). Baldini et al. describe the clinical association between Vit and AITD and evaluate the possible common molecular pathways involved in their pathogenesis.

Lichen planus (LP) and lichen sclerosus (LS) are cutaneous-mucous disorders, too. Their etiology is unknown, clinical and histological data suggest an autoimmune pathogenesis; however only few papers evaluated their association with AITD. Guarneri et al. review the scientific literature about the correlation between AITD and lichen, and the genetic risk factors in common between these conditions.

Myasthenia gravis (MG) is a neuromuscular disease caused by a deficient transmission of the nerve impulse to muscles, leading to muscle weakness and exaggerated fatigue, that is mediated by autoantibodies. AITD and MG are frequently associated; their etiology is multifactorial and depends on genetic and environmental factors. The review by Lopomo and Berrih-Aknin focuses on AITD and MG, their common features and their diversities.

The association between CAG and AITD has been first shown at the beginning of 1960s, and recently has been included in polyglandular autoimmune syndrome type IIIb (10). Cellini et al. summarize the most recent achievements on this peculiar association.

Santoro et al. evaluate the association between AT and glomerulopathies. IgA nephropathy, membranous nephropathy, membranoproliferative glomerulonephritis, focal segmental glomerulosclerosis, amyloidosis, minimal change disease, and antineutrophil cytoplasmic autoantibody (ANCA) vasculitis are renal disorders frequently observed in AT. Different hypotheses have been reported about the association between AITD and glomerulopathies. A probable mechanism at the basis of the association between ANCA vasculitis and AT is the cross-reactivity between antigens in presence of a genetic predisposition.

Moreover, this Research Topic evaluates also thyroid autoimmunity during the complex period after childbirth, that is critical for the *de novo* appearance or exacerbation of autoimmune diseases, and AITD. Di Bari et al. describe the postpartum thyroid diseases that consist of postpartum thyroiditis (PPT), but also GD and non-autoimmune thyroiditis.

Postpartum mood disorders are a common form of maternal psychiatric morbidity, owing to the rapid endocrine and psychological alterations in the postpartum period (11). Le Donne et al. discuss the interaction between thyroid autoantibodies and mood disorders.

Antiphospholipid syndrome (APS) is an autoimmune disorder manifesting as recurring venous or arterial thrombosis that can induce complications during pregnancy and is associated with the presence of persistent antiphospholipid (aPL) autoantibodies. Versini conducts a literature review on the present data on aPL/APS and AITD, and particularly on the role of this association in obstetrical complications.

The exact pathogenetic mechanisms underlying the above reported disorders are not completely known. The effect of genetic on the association of different autoimmune disorders has been shown, as: (a) there is significant clustering of AITD within families (40–50% of AT patients have another family member with AT) (12); (b) a clear evidence comes from twin studies for GD (13) and AT (14) with concordance rates of 30–40% in monozygotic twins and 0–7% in dizygotic twins.

Moreover, new recent insights in genome-wide association studies (GWAS) about autoimmune and immune-mediated diseases have increased the knowledge of the pathogenesis underlying these disorders (15), suggesting a common genetic susceptibility (15).

Environmental factors [selenium, and vitamin D deficiency, high iodine intake, exposure to radiation (owing to nuclear fallout or medical irradiation)] are of particular importance for the appearance of AITD in susceptible subjects (16). Cigarette smoking is associated with GD and Graves' ophthalmopathy (GO), although it reduces the risk of hypothyroidism and thyroid autoimmunity. Also viral infections can drive AITD, in particular human parvovirus B19 (EVB19) and HCV. Regarding the various existing chemical contaminants, pesticides and halogenated organochlorines differently disrupt thyroid function. Polychlorinated biphenyls and their metabolites and polybrominated diethyl ethers bind to thyroid transport proteins (i.e., transthyretin), displace thyroxine, in this way disrupting thyroid function. Considering drugs, interferon- and medicines containing iodine have been associated with AITD. These environmental issues have been presented in a recent paper by Ferrari et al. (16).

A prevalent Th1 immune pattern has been shown in patients with AT, GD, GO (17, 18), type 1 diabetes, SLE, SSc, RA, MC, and others (19), in the initial phase of these disorders. Furthermore, in GD, GO, SLE, MC (and others) a Th1 prevalence has been shown in the active phase, that switches to a Th2 profile in the inactive phase (20, 21) of the disease. So it has been hypothesized that the influence of genetic and environmental factors could lead to the onset of autoimmune phenomena in different organs in the same subject (1), characterized by predominance of a Th1 immune pattern at the beginning, and in the active phase of these disorders.

In conclusion, an association of other autoimmune diseases in patients with thyroid autoimmunity has been shown, and this Research Topic provides an extensive update of the literature, and suggests interesting points for new investigations.

AUTHOR CONTRIBUTIONS

AA and SB gave substantial contribution in writing the article, and revised it critically for important intellectual content. AA and SB agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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MINI REVIEW
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Epigenetics and Autoimmune Thyroid Diseases

*Fabio Coppedè**

Department of Translational Research and New Technologies in Medicine and Surgery, Section of Medical Genetics, University of Pisa, Pisa, Italy

Increasing evidence suggests that epigenetic modifications, including changes in DNA methylation, covalent modifications of histone tails, and gene silencing mediated by non-coding RNA molecules, play a substantial role in the pathogenesis of autoimmune disorders and might be seen as the result of environmental insults that trigger these conditions. Studies in cells and tissues of patients with autoimmune thyroid diseases (AITD), and particularly in Graves' disease (GD) and Hashimoto's thyroiditis (HT), are increasingly revealing altered epigenetic marks and resultant deregulation of gene expression levels, but the available data are still limited to be translated into the clinical settings. Particularly, genome-wide methylation and histone tail modification screenings are limited to a few studies in GD patients, and the diagnostic values of the observed epigenetic changes or their potential prognostic utility are still unclear. Similarly, data concerning microRNA expression in AITD patients are largely descriptive and not yet translated into the clinics. In addition, studies relating certain environmental exposures to specific epigenetic changes in AITD and studies evaluating the crosstalk between different epigenetic mechanisms are largely missing. In summary, despite that there is a clear evidence of epigenetic impairment in AITD, further research is required for a better understanding of the epigenetic networks involved in disease pathogenesis, thereby opening the way for potential diagnostic and prognostic tools, as well as for epigenetic interventions in the patients.

Keywords: autoimmune thyroid diseases, Graves' disease, Hashimoto's thyroiditis, epigenetics, DNA methylation, non-coding RNAs, microRNA, histone tail modifications

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Edited by:
Alessandro Antonelli, University of Pisa, Italy

Reviewed by:
Roberto Vita, University of Messina, Italy
Flavia Di Bari, Policlinico di Messina, Italy

***Correspondence:**
Fabio Coppedè
fabio.coppede@med.unipi.it

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INTRODUCTION

Epigenetics is an umbrella term referred to heritable and reversible marks, such as DNA methylation or covalent modifications of histone tails, that regulate the chromatin structure and switch genes "on" and "off" without changing the primary DNA sequence (1). In addition, several classes of non-coding RNAs, ranging from small to long molecules, play a substantial role in the epigenetic regulation of gene expression (2). Some studies performed at the end of the last century revealed that CD4+ T cells treated with 5-azacytidine, a substance that inhibits DNA methylation, respond to the presentation of self antigens and cause a lupus-like syndrome when injected in mice (3, 4), suggesting that epigenetic mechanisms, and particularly impaired DNA methylation, could be involved in autoimmune reactions (3, 4). A few years ago, we reviewed the literature for studies addressing epigenetic modifications in autoimmune diseases, most of them were focused on systemic lupus erythematosus or rheumatoid arthritis (RA), but increasing evidence was available for other autoimmune

pathologies, including autoimmune thyroid diseases (AITD), a group of disorders characterized by loss of immunological self-tolerance (5). The major AITD are Graves' disease (GD) and Hashimoto's thyroiditis (HT), both organ-specific autoimmune diseases characterized by lymphocytic infiltration of the thyroid gland with accompanying evidence of humoral and cellular immune system activation and female preponderance (6). In GD, the autoimmune process results in the production of thyroid-stimulating antibodies leading to hyperthyroidism, whereas in HT the immune response is destructive, leading in most cases to hypothyroidism (7). Genetic predisposition and environmental factors, such as infection, chemicals, and nutrition, play a role in the pathogenic process of autoimmunity (8). Recent studies have clearly demonstrated a significant increased risk of other autoimmune diseases in patients with AITD and there is evidence of genetic factors that influence the association of different autoimmune disorders (9). In this regard, the investigation of the genetic risk factors for AITD has revealed that some genes are unique for GD or HT, while others are common to both diseases or to AITD and other autoimmune diseases (10). Increasing evidence suggests that epigenetic modifications may be seen to bridge the gap between genetics and the environment (10, 11), so that epigenetic modifications of autoimmune-related genes, resulting from environmental exposure, are increasingly recognized to play a pivotal role in autoimmunity (5). This article critically discusses the most recent evidence of epigenetic modifications in AITD.

DNA METHYLATION IN AITD

DNA methylation consists of the addition of a methyl group to the DNA, mediated by enzymes called DNA methyltransferases (DNMTs). The best-characterized DNA methylation process is the addition of a methyl group to cytosine in a CpG dinucleotide context, forming 5-methylcytosine (5-mC). When the promoter region of a gene is methylated, the expression of that gene is repressed because methyl-CpG-binding domain (MBD) proteins recognize and bind to the methylated DNA and, in turn, recruit other epigenetic factors to enhance chromatin remodeling and transcriptional repression (12–14). DNA methylation is a physiological mechanism required for several cellular processes, including genomic imprinting, embryonic development, cell differentiation, X chromosome inactivation, repression of repetitive elements, and maintenance of the cellular identity (1).

Skewed X Chromosome Inactivation (XCI) in AITD

Many, but not all, autoimmune diseases are more common in females than in males, with reported ratios ranging from 10:1 to 3:1 (15). A possible role of skewed XCI, mediated by epigenetic mechanisms, has been suggested in the etiology of AITD (16), RA (17), and scleroderma (18) to partially explain the female preponderance. The X chromosome contains several immune-related genes, including CD40 ligand (*CD40L*), forkhead box P3 (*FOXP3*), and toll-like receptor 7 (*TLR7*), and one of the two X chromosomes in each female cell is randomly inactivated by methylation to balance gene expression levels between males, that possess only one X chromosome, and females who have two copies of the X chromosome (19). In some females, however, this inactivation can predominantly occur to either the maternal or paternal X chromosome, and this phenomenon is referred to as skewed XCI (19). Concerning AITD, studies performed over the last two decades have addressed the link between skewed XCI and AITD risk (16, 17, 20–23). A meta-analysis of those studies confirmed significant skewing of XCI with GD and HT (23), and studies on twins revealed that skewed XCI may be causally associated with clinically overt AITD, but not with the presence of thyroid autoantibodies in euthyroid subjects (7). A more recent study in AITD patients revealed that the proportion of skewed XCI was not significantly different with respect to control subjects, but was higher in patients with intractable GD than in those with GD in remission, and in patients with severe HT than in those with mild HT, suggesting that skewed XCI is likely related to the prognosis of AITD, rather than to their development (19).

Polymorphisms of Genes Involved in DNA Methylation and AITD Risk

DNA methylation depends on the cellular availability of dietary folates and related B-group vitamins, all required for the production of S-adenosylmethionine, the intracellular donor compound of methyl groups (24). Several investigators provided indirect evidence of impaired DNA methylation in AITD by addressing the role of genes involved in folate metabolism and DNA methylation reactions as genetic risk factors for AITD. Particularly, those studies investigated polymorphisms in *DNMT* genes or in methylenetetrahydrofolate reductase (*MTHFR*) and methionine synthase reductase (*MTRR*) genes, the two latter coding for folate-metabolizing enzymes (25, 26). rs1801133 in *MTHFR* was associated with reduced GD risk in women (25), while rs2228612 in *DNMT1* was linked to DNA hypomethylation and with the intractability of GD and rs1801394 in *MTRR* with the severity of HT (26). A more recent study addressed the contribution of *DNMT* gene polymorphisms in a large cohort of AITD patients composed by a total of 685 GD patients, 353 HT patients, and 909 healthy controls, revealing that both rs2424913 in *DNMT3B* and rs2228611 in *DNMT1* were associated with AITD susceptibility (27). Interestingly, *DNMT* gene polymorphisms have been associated with other autoimmune disorders, for example *DNMT3B* polymorphisms were linked to increased risk of oral lichen planus (28), with the progression of joint destruction in RA (29), and with increased risk of thymoma in patients with myasthenia gravis (30). Collectively those studies suggest that variants in *DNMT* genes might account for a shared susceptibility to various autoimmune disorders.

Evidence of Impaired DNA Methylation in AITD

More direct evidence of impaired DNA methylation in AITD came from recent epigenetic screenings in blood samples, lymphocytes, and thyrocytes from the patients (**Table 1**). A genome-wide screening in peripheral blood cells of three GD patients and three age- and gender-matched controls revealed 82 hypermethylated and 103 hypomethylated genes in GD patients

TABLE 1 | Epigenetic studies in patients with AITD.

Endpoint	Tissue	Disease	Findings	Reference
DNA methylation	PBMC	GD	Genome-wide screening revealed 82 hypermethylated and 103 hypomethylated genes	(31)
DNA methylation	CD4+ and CD8+ T cells	GD	Genome-wide screening revealed 365 and 3,322 differentially methylated sites in CD4+ and CD8+ T cells, respectively	(32)
DNA methylation	Thyroid gland	AITD	Impaired methylation and increased expression of the *ICAM1* gene	(33)
Histone tail modifications	PBMC	GD	Global reduction of histone 4 acetylation	(36)
Histone tail modifications	CD4+ and CD8+ T cells	GD	Reduction of histone 3 lysine 4 trimethylation (H3K4me3) and histone 3 lysine 27 acetylation (H3K27ac)	(32)
MicroRNA (miRNA) expression	PBMC	GD	No expression of miR-154*, miR-376b, and miR-431* in early disease stages	(39)
MiRNA expression	Serum	HT	Increased levels of miR-22, miR-375, and miR-451	(40)
MiRNA expression	Serum	GD	Increased levels of miR-16, miR-22, miR-375, and miR-451	(36)
MiRNA expression	CD4+ and CD8+ T cells	HT and GD	Differential expression of miR-200a and miR-155	(40)
MiRNA expression	Serum	GD	Correlation between circulating levels of miR-155 and miR-146a and Grave's ophtalmopathy	(42, 43)
MiRNA expression	Plasma and CD4+ T cells	GD	Upregulation of Bcl-6 and downregulation of miR-346	(44)
MiRNA expression	PBMC and thyroid gland	HT	Downregulated miR-125a-3p expression resulting in upregulation of interleukin-23 receptor levels	(45)
MiRNA expression	PBMC	HT	Increased let-7e expression regulates interleukin 10 expression	(46)
MiRNA expression	Thyroid gland	HT	Increased miR-142-5p expression regulates claudin-1 expression	(47)
MiRNA expression	Thyroid gland	GD	Altered expression of 23 miRNAs with resulting deregulated expression of more than 2,000 messenger RNAs	(48)

AITD, autoimmune thyroid diseases; GD, Graves' disease; HT, Hashimoto's thyroiditis; PBMC, peripheral blood mononuclear cells.

(31). Among them, the authors identified some candidate genes already associated to GD or other autoimmune diseases, such as the immunoregulatory factor *ADRB2* (hypermethylated), *ICAM1* (hypomethylated) coding for a glycoprotein of cell surface named intercellular adhesion molecule 1, *B3GNT2* (hypermethylated) involved in the regulation of lymphocyte activity, and others (31). Besides, the transcription of DNMT1 and MECP2 (a MBD protein) at the messenger RNA (mRNA) level was significantly decreased in GD patients compared with normal controls (31). Another genome-wide analysis of DNA methylation was performed in CD4+ and CD8+ T cells of 38 GD patients and 31 matched controls. The study revealed 365 and 3,322 differentially methylated CpG sites in CD4+ and CD8+ T cells, respectively (32). Among the hypermethylated CpG sites, the authors found enrichment of genes involved in T cell signaling (*CD247*, *LCK*, *ZAP70*, *CD3D*, *CD3E*, *CD3G*, *CTLA4*, and *CD8A*) and decreased expression of CD3 gene family members (32). Furthermore, the authors observed hypermethylation of the first intron of the thyroid-stimulating hormone receptor (*TSHR*) gene, a gene that contains several GD-associated polymorphisms (32). A more recent study revealed aberrant DNA methylation of the *ICAM1* gene promoter, associated with increased gene expression, in the thyrocytes of 35 AITD patients with respect to 35 sex- and age-matched controls (33).

HISTONE TAIL MODIFICATIONS IN AITD

Several posttranslational modifications occur on the histone tails of nucleosomes and are associated with either open or condensed chromatin structure. Collectively those modifications are involved in the regulation of gene expression, as well as in DNA repair, replication, and recombination processes, and include acetylation, methylation, phosphorylation, ubiquitylation, sumoylation, and other covalent modifications that directly influence the overall chromatin structure or regulate the binding of effector molecules (34). Among them, acetylation and methylation on histone tail residues represent the two best-characterized epigenetic marks regulating the chromatin structure (35). Histone tail acetylation is mediated by histone acetyltransferases and results in an open chromatin structure that allows transcription (35, 36). Histone tail methylation of core histones H3 and H4 can be associated with either chromatin condensation or relaxation, due to the fact that several sites for methylation are present on each tail (35, 36).

Little is known about histone tail modifications in AITD (**Table 1**). A pilot study in peripheral blood mononuclear cells (PBMC) of GD patients revealed reduced global histone H4 acetylation levels coupled with increased levels of histone deacetylase proteins with respect to healthy controls (36). Furthermore, the previously described genome-wide DNA methylation analysis

in CD4+ and CD8+ T cells of GD patients (32) revealed that the hypermethylation of genes involved in T cell signaling was accompanied by decreased levels of H3K4me3 (histone 3 lysine 4 trimethylation) and H3K27ac (histone 3 lysine 27 acetylation), both marks usually found in nucleosomes that flank active promoters (32). Collectively, those studies confirm that gene promoter methylation observed in cells of GD patients is coupled to changes in the chromatin structure to allow the silencing of gene expression.

NON-CODING RNAs IN AITD

A growing body of evidence suggests impaired expression of non-coding RNAs, and particularly of microRNAs (miRNAs) in autoimmune diseases (33). MiRNAs are small RNA molecules ranging from 18 to 25 nucleotides in length that bind to the 3′ untranslated region of target mRNAs and mediate their post-transcriptional regulation, leading to either degradation or translational inhibition, depending on the degree of sequence complementarity (37). MiRNAs target about 60% of all genes, and interact with other epigenetic mechanisms, such as DNA methylation and histone tail modifications, to organize the whole gene expression profile (38). Early studies in the field revealed several miRNAs that were differently expressed in cells from patients with AITD than in cells from healthy subjects (**Table 1**). For example, it was observed that the expression of miR-154*, miR-376b, and miR-431* was suppressed in PBMC from initial GD patients with respect to healthy controls, but recovered in GD patients in remission (39). Others observed that serum levels of miR-22, miR-375, and miR-451 were increased in patients with HT compared with healthy subjects and that serum levels of miR-16, miR-22, miR-375, and miR-451 were increased in patients with GD (40), while another study revealed significant variations of miR-200a and miR-155 in purified CD4+ T-cells and CD8+ T-cells of patients suffering from GD and HT (41). More recent studies attempted to explain the biological significance of miRNA deregulation or their possible clinical implications in AITD (42–46). For example, it has been proposed that increased miR-155 and decreased miR-146a may promote ocular inflammation and proliferation in Graves' ophthalmopathy (42) and that circulating levels of miR-146a and interleukin 17 are significantly correlated with the clinical activity of Graves' ophthalmopathy (43). It was also observed that miR-346 regulates CD4(+)CXCR5(+) T cells by targeting Bcl-6, a positive regulator of follicular helper T cells, and might play an important role in the pathogenesis of GD (44). Similarly, a decreased expression of miR-125a-3p was shown to upregulate interleukin-23 receptor levels in patients with HT (45). Increased expression levels of the miRNA let-7e were observed in PBMC of HT patients compared with those in GD patients and healthy volunteers, and it was shown that let-7e may be associated with the pathogenesis of HT through the regulation of intracellular interleukin 10 expression (46).

Limited data are available concerning miRNA expression in the thyroid gland of AITD patients. In this regard, miR-142-5p, miR-142-3p, and miR-146a showed high expression in HT thyroid gland (47). Furthermore, miR-142-5p was also detected in HT patient serum and positively correlated with thyroglobulin antibody (47). In addition, the overexpression of miR-142-5p in HT thyrocytes resulted in reduced claudin-1 mRNA and protein levels (47). Claudin proteins are major constituents of the tight junction complexes that regulate the permeability of epithelia, and miR-142-5p-mediated reduced expression of claudin-1 led to an increased permeability of thyrocytes monolayer (47). Another study showed a differential expression of 23 miRNAs in thyroid tissue of GD patients, resulting in the upregulation of 1,271 mRNAs and in downregulated expression of 777 mRNAs (48). Particularly, an integrated analysis of differentially expressed miRNAs and their target mRNAs demonstrated that miR-22 and miR-183 were increased in thyroid tissue of GD patients while their potential target mRNAs were decreased. On the contrary, miR-101, miR-197, and miR-6 were decreased while their potential target mRNAs were increased (48).

Indirect evidence of a possible involvement of miRNAs in AITD pathogenesis came also from studies linking polymorphisms in miRNA genes to increased AITD risk (49–51), so that there is increasing interest to clarify the variability in miRNA expression in order to better discriminate between miRNAs that are deregulated in a given disease, from others that could account for several autoimmune disorders (52, 53). In this regard, a deeper understanding of miRNA mediated networks in autoimmune diseases and their crosstalk with other epigenetic mechanisms that regulate gene expression levels is fundamental to elucidate the potential translational implications of these biomarkers (52, 53). In addition, there is increasing evidence that other non-coding RNAs than miRNAs, such as for example long non-coding RNAs, might play a role in autoimmune diseases, even if evidence in AITD is still limited (54).

CONCLUDING REMARKS

Autoimmune thyroid disease patients can be clinically categorized into those with hyperthyroidism (GD), those with hypothyroidism (HT), and euthyroid subjects harboring thyroid autoantibodies (7). However, despite their phenotypic differences, it is believed that AITD patients share some common etiological factors (7), and genetic studies have revealed that if certain genes are unique for GD or HT, others are common to both disorders or to AITD and other autoimmune diseases (10). Indeed, different AITD phenotypes are often seen in members of the same family (7), and a significant increase in the prevalence of certain other autoimmune disorders has been reported in AITD patients (9). Epigenetic changes have been observed in multiple autoimmune diseases, they can be induced by environmental factors, and are increasingly recognized as one of the mechanisms by which environmental factors can trigger autoimmunity (10, 11). In this regard, there is increasing interest in searching for epigenetically deregulated pathways that might be common to different autoimmune disorders, and others that characterize a given disease and might be relevant in the clinical setting for diagnostic, prognostic, and therapeutic purposes (5). For what is concerning AITD there is increasing evidence of epigenetic changes in these conditions, but the available studies are still limited (**Table 1**) to be translated into the clinical settings. Particularly, the two available

genome-wide DNA methylation studies in blood AITD cells are limited to GD patients (31, 32), and one of them included only three patients and three matched controls (27) making it difficult to clearly discriminate disease-specific epigenetic changes from others that could result from interindividual variability. Also data concerning histone tail modifications are mainly available from GD patients (32, 36), and lack of similar epigenome-wide data in cells from HT individuals does not allow comparing the two conditions in terms of epigenetic differences or similarities, so that the diagnostic values of the observed epigenetic changes and their potential prognostic utility are not yet clearly defined. Furthermore, methylation data in thyroid cells of AITD patients are limited to the study of a single gene (33). Data concerning miRNA expression in cells and tissues from AITD patients have been largely descriptive, and even if some investigators attempted to evaluate their potential clinical utility (42–46), data are still limited to be translated into the clinics. Epigenetic data are also lacking for another AITD, the postpartum thyroiditis, in contrast with postpartum psychosis, concerning which a study on miRNA expression was carried out (55). In this study, changes in miR-146a and miR-212 expression were observed in the 20 recruited patients with postpartum psychosis, but only 3 patients developed autoimmune thyroiditis, the small number impeding statistical analysis (55).

In addition, at best of my knowledge, data linking environmental exposures to specific epigenetic changes in AITD as well as studies evaluating the crosstalk between different epigenetic mechanisms are largely missing.

In conclusion, many investigators observed epigenetic changes in cells from AITD patients, but additional studies are required to confirm the observed changes and relate them to altered pathways that could be peculiar of a certain disease or of a certain environmental exposure, as well as to clarify common pathways in autoimmunity that could justify the onset of different autoimmune phenotypes in related family members, or in the same individual, in relation to different environmental exposures. Therefore, further research in this field could lead to a better understanding of the networks involved in disease pathogenesis, thereby opening the way for potential diagnostic and prognostic tools, as well as for epigenetic interventions in the patients based on miRNA silencing and/or chromatin remodeling agents.

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Hashimoto's Thyroiditis and Autoimmune Gastritis

*Miriam Cellini, Maria Giulia Santaguida, Camilla Virili, Silvia Capriello, Nunzia Brusca, Lucilla Gargano and Marco Centanni**

Endocrinology Unit, Department of Medico-Surgical Sciences and Biotechnologies, Sapienza University, Latina, Italy

The term "thyrogastric syndrome" defines the association between autoimmune thyroid disease and chronic autoimmune gastritis (CAG), and it was first described in the early 1960s. More recently, this association has been included in polyglandular autoimmune syndrome type IIIb, in which autoimmune thyroiditis represents the pivotal disorder. Hashimoto's thyroiditis (HT) is the most frequent autoimmune disease, and it has been reported to be associated with gastric disorders in 10–40% of patients while about 40% of patients with autoimmune gastritis also present HT. Some intriguing similarities have been described about the pathogenic mechanism of these two disorders, involving a complex interaction among genetic, embryological, immunologic, and environmental factors. CAG is characterized by a partial or total disappearance of parietal cells implying the impairment of both hydrochloric acid and intrinsic factor production. The clinical outcome of this gastric damage is the occurrence of a hypochlorhydric-dependent iron-deficient anemia, followed by pernicious anemia concomitant with the progression to a severe gastric atrophy. Malabsorption of levothyroxine may occur as well. We have briefly summarized in this minireview the most recent achievements on this peculiar association of diseases that, in the last years, have been increasingly diagnosed.

Keywords: thyroiditis, polyglandular autoimmune syndrome, thyroxine malabsorption, gastric atrophy, pernicious anemia, *Helicobacter pylori* infection, cellular immunity

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***Correspondence:**
Marco Centanni
marco.centanni@uniroma1.it

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INTRODUCTION

The thyrogastric syndrome was initially described in the early 1960s and initially characterized by the presence of thyroid autoantibodies in patients with pernicious anemia, the latter being used as synonymous for atrophic gastritis (1). More recently, the autoimmune gastritis has been better characterized classifying chronic atrophic gastritis, with or without the PA, based on the histological evaluation and the presence of serum parietal cell (PCA) and/or intrinsic factor (IFA) autoantibodies (2, 3). Based on these criteria, the association between autoimmune thyroid disorders and chronic autoimmune gastritis (CAG) has also been reassessed (4, 5) and nowadays is included in the adult form of polyglandular autoimmune syndrome (PAS), characterized by two or more endocrine and non-endocrine autoimmune disorders (6). In particular, Betterle and colleagues have proposed the inclusion of thyrogastric syndrome in the PAS Type 3b, in which Hashimoto's thyroiditis (HT) occurs also associated with non-endocrine autoimmune gastrointestinal disorders and where it plays a pivotal role (7, 8). This is in keeping with the

evidence that chronic autoimmune thyroiditis represents the more prevalent autoimmune disorder worldwide making the frequency of thyrogastric syndrome quite high (4). This notion is supported by the high percentage (12–40%) of positivity of PCA in adult patients with HT (9) which, in turn, is present in approximately 40% of patients with atrophic gastritis (10). Besides the fact that the thyroid and the stomach share some embryological and biochemical features (11), some intriguing similarities have been observed even in the putative pathogenic mechanisms, which characterize the thyrogastric syndrome (12). Furthermore, some specific clinical features characterize or lead to the suspicion of the coexistence of both thyroid and gastric autoimmune (13, 14) disorders. These similar peculiar features will be briefly described in this minireview.

THYROID AND STOMACH: EMBRYOLOGIC DERIVATION AND ROLE of Na^+/I^- SYMPORTER

The thyroid gland and stomach, despite the different localization and function, share some similar morphologic and functional characteristics, likely due to their common embryologic origin (11). In fact, the thyroid gland develops from the primitive gut and therefore thyroid follicular share with parietal cells the same endodermal origin. Also, both these cells are polarized and are characterized by the presence of apical microvilli housing enzymatic activities.

Furthermore, gastric mucosal and thyroid follicular cells both show the ability to concentrate and transport iodine across the cell membrane (15). This process is mediated by the Na^+/I^- symporter (15) and involves similar enzymes with an efficient peroxidase activity (12) (**Table 1**). Furthermore, besides its essential role for the synthesis of thyroid hormones, iodine regulates the proliferation of gastric mucosal cells (16). In fact, in the presence of gastric peroxidase, iodine acts as an electron donor and participates in the removal of free oxygen radicals, thus playing an antioxidant action (17). These effects may explain the regulatory role of iodine in the proliferation of mucosal cells and its protective role against gastric carcinogenesis (11, 16). This hypothesis has been confirmed by the reported link among iodine deficiency, goiter, and increased risk of developing gastric cancer (18).

TABLE 1 | Shared characteristics between thyroid and stomach.

Embryological origin	• Primitive gut for both thyroid and stomach
Cell features	• Presence of cells polarity • Cells characterized by apical microvilli
Biochemical features	• Presence of Na^+/I^- symporter (sodium-iodide symporter) • Presence of peroxidase isoenzymes (TPO and GPO)
Function	• Ability to concentrate iodine • Presence of antioxidative activities • Secretion of mucinous glycoproteins: thyroglobulin and mucine
Pathogenesis	• Cellular immune involvement • Similarity of autoaggressive processes • Mechanisms of cellular damage • Expression of autoantigens and related cross-reacting autoantibodies
Pathology	• Clinically related autoimmune disorders • Peculiar associative clinical features

CHRONIC AUTOIMMUNE/HASHIMOTO'S THYROIDITIS AND CAG

Chronic lymphocytic thyroiditis is the most frequent autoimmune disorder and represents the prototype of organ-specific autoimmunity (19). Its prevalence, despite some difference of sex, age, race, and iodine intake, reaches about 5% in the general population (20). Much less frequent is the chronic autoimmune atrophic gastritis (type A gastritis or body/fundus gastritis), which represents only some 5% of the whole spectrum of chronic gastritis and must be differentiated from the one associated with chronic *Helicobacter pylori* (Hp) infection (type B gastritis or antral gastritis) (21, 22). HT is characterized by diffuse inflammatory changes with lymphocytic infiltration of the thyroid gland, leading to the destruction of the thyroid epithelial cells with subsequent fibrosis (23). Similarly, autoimmune gastritis is a chronic inflammatory disease involving gastric body and fundus, with the progressive reduction and/or disappearance of the native gastric glands that are sometimes replaced by intestinal or pyloric epithelium (metaplasia) (3). The natural history of HT is the progressive reduction of thyroid function till overt hypothyroidism (24) with a rate of progression of 2–4% per year (23), while that of gastric atrophy features the progressive reduction, till disappearance, of parietal cells, leading to reduced or absent acid production (3, 22). These alterations interfere with absorption of essential nutrients leading, at first, to iron-deficient anemia, followed by PA if the self-injurious process involves the IFA (13). Increased risk of developing neuroendocrine tumors and gastric adenocarcinoma is also associated with the severity of damage of gastric mucosa (22).

Pathogenesis

Both these autoimmune disorders are characterized by a complex interaction between genetic susceptibility and environmental factors that results in the loss of immune tolerance to self-antigens and in the development of autoimmune diseases. The loss of immune tolerance may involve alteration both in the central tolerance with reactive T cells escaped from intrathymic deletion and in the peripheral tolerance as in the case of defective T regulatory lymphocytes (25, 26). Genetic susceptibility has been confirmed for both diseases since their incidence is higher among identical twins and first-degree relatives as well as their presence may be observed in association with further autoimmune disorders (6, 7, 20, 26). Both of these disorders show a definite association with different HLA aplotypes; in HT, it has also been proven that the involvement of many other immunoregulatory genes (27), while this issue has not been elucidated in the pathogenesis of human autoimmune gastritis (26).

Several environmental factors seem to be involved in the pathogenesis of HT (excessive iodine intake, selenium deficiency, and specific drugs use), while very weak evidence supports a role for infectious agents as trigger for this disease (hepatitis C virus, HHV-6, and Yersinia) (27). The role of environmental factors

in triggering autoimmune gastritis has been more studied and a stronger link between *H. pylori* infection and CAG has been detected, despite not sufficient to establish a causative relationship between these two diseases (21). *H. pylori* infection affects approximately 50% of the world population and is in turn the most common cause of chronic gastritis. At first, the *H. pylori* infection involves the gastric antrum, but in some patients it may extend into the gastric body (pangastritis) and, in genetically predisposed individuals, it may be a trigger for autoimmune atrophic gastritis, being this hypothesis still debated (3, 28, 29). The pathogenic link may be found in a cross-reactivity mechanism (molecular mimicry) (30): in fact, the Hp infection may induce the proliferation of $CD4^+$ T lymphocytes that recognize epitopes of *H. pylori* structurally similar to those of H^+/K^+ATPase, an enzyme found on the apical membrane of parietal cells (31). Indeed, dendritic cells may present these shared epitopes to naïve T cells and, in the absence of peripheral tolerance, a Th1-driven autoreactive clone is activated (28). Again, the cellular immune mechanisms of autoimmune thyroiditis show some similarities with those of CAG. In HT, inflammation leads to secretion of IFN-γ, a cytokine turning thyrocytes into antigen-presenting cells (32). The variation of costimulatory factors that drive the binding between an autoantigen and the T-cell receptor allows the proliferation and polarization of autoreactive effector lymphocytes (27). Due to a Th17 cell polarization, the inflammatory process and the subsequent fibrosis seem to prevail in the early phase of thyroiditis (33); in a later phase, when the lymphocytic infiltration and the parenchymal destruction are prevalent, a polarized Th1 profile has been reported (34, 35). The Th1 lymphocytes are able to aid cytotoxic T-lymphocytes and to produce specific cytokines (TNF-α and IFN-γ) able to induce the cellular apoptosis (35) in thyroid cells. The association of a gastric autoimmune disorder has been shown to add a Th2 cytokine profile to the described ones (36). The precise mechanism leading to thyrocytes and/or parietal cell death is still unknown. However, the involvement of Fas upregulation in thyrocytes, due to IL-1beta produced by activated macrophages, has been proven (37). Normal thyrocytes, in fact, express FasL but not Fas, while their concomitant expression induces an autocrine interaction that may represent the main mechanism inducing apoptosis (37). In experimental autoimmune gastritis, also parietal cells express Fas that, in this case, could trigger apoptosis by binding Fas-ligand on infiltrating T cells (28). Following cells damage, the production of specific autoantibodies ensues in epiphenomenal fashion (34). Cellular and humoral immune cooperation characterizes both autoimmune thyroiditis and gastritis leading to the production of specific autoantibodies (antithyroperoxidase, antithyroglobulin, and antiparietal cell antibodies). These autoantibodies are of paramount importance in the diagnosis but of little, if any, in the pathogenesis of these autoimmune disorders.

CLINICAL ASPECTS OF THYROGASTRIC SYNDROME

Clinical pathological aspects of this association are attributable to malabsorption of iron and thyroxine, both linked to a reduced gastric acid secretion.

Iron Deficiency and PA

Chronic atrophic gastritis is clinically silent in most cases and only a small percentage of patients may complain about dyspeptic symptoms. A well-described clinical feature of thyrogastric syndrome is represented by the presence of an iron-deficient and/or a PA. In fact, it has been demonstrated that an iron-deficient anemia, refractory to oral iron therapy, in patients with HT, may be due to chronic atrophic gastritis (13). The clinical signs of this disease appear after several years of its onset, when the progressive reduction to disappearance of the parietal cells leads to atrophy of the gastric mucosa, impairing the absorption of iron, vitamin B12 (cobalamin), folate, and other nutrients (22). At the physiologic acid pH (1.5–2) of the stomach, ascorbic acid, the most active form of vitamin C, allows iron reduction from the nutritional ferric (Fe +++) to the ferrous form (Fe ++), thus forming a complex that drives the absorption in the upper portion of the small intestine (22). In the initial phase of the atrophic gastritis, the damage of parietal cells can lead to iron deficiency microcytic anemia as the only clinical sign (38). When the gastric atrophy becomes severe and/or the IFA is no longer produced, even the absorption of cobalamin becomes compromised. Besides hydrochloric acid that promotes the separation of vitamin B12 from food, the parietal cells also produce the IFA that binds cobalamin and pipes it to the distal ileum, where it is absorbed following a binding to specific receptors (39). Vitamin B12 deficiency is responsible for hematologic changes (macrocytic anemia) and specific neurological disorders (paresthesia and neuritis) which are peculiar of PA (22).

Thyroxine Malabsorption in Chronic Gastritis

The worldwide used pharmaceutical form of thyroxine (sodium levothyroxine, T_4) is obtained by native hormone through its salification with sodium hydroxide. The absorption of T_4 occurs in all sections of small intestine being anyway incomplete and ranging from 62 to 82% of the ingested dose (40). However, increasing evidence of a relevant role of the intact gastric acid secretion on the subsequent intestinal absorption of sodium levothyroxine has been reported in the last years (41). In fact, an increased therapeutic T4 dose has been described in patients with gastric disorders (Hp infection, chronic gastritis, gastric atrophy) or chronically treated with proton pump inhibitors or in non-fasting patients (41–43). All these conditions are characterized by a modified gastric pH that may affect T4 absorption by changing the ionization status, as already described for iron, or the dissolution process of the pharmaceutical T4 form. Furthermore, *in vitro* studies have shown the pH dependency of the dissolution profile of different T4 preparations (44). This evidence boosted the research for novel thyroxine formulations as liquid or softgel capsules. These ones showed, as compared to the classic tablet formulation, a similar or better bioavailability as well as a lower number of excipients (45, 46). In clinical studies, softgel or liquid formulations performed better in patients with gastric disorders (47, 48) and in proton pump inhibitors users (49, 50).

In conclusion, the association of thyroid and gastric autoimmune disorders represents a frequent syndrome, included in the autoimmune polyendocrine syndrome. The similar or even common biochemical and pathogenic features fully support the term thyrogastric disease described some 60 years ago. From a clinical standpoint, the presence of iron-deficient anemia and thyroxine malabsorption may represent an alert signal for the presence of a gastric disorder in patients with thyroid autoimmunity and should trigger a specific diagnostic workup.

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All authors listed have made substantial, direct, and intellectual contribution to the work and approved it for publication.

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Vitiligo and Autoimmune Thyroid Disorders

*Enke Baldini[1], Teresa Odorisio[2], Salvatore Sorrenti[1], Antonio Catania[1], Francesco Tartaglia[1], Giovanni Carbotta[1], Daniele Pironi[1], Roberta Rendina[3], Eleonora D'Armiento[3], Severino Persechino[4] and Salvatore Ulisse[1]**

[1] Department of Surgical Sciences, "Sapienza" University of Rome, Rome, Italy, [2] Laboratory of Molecular and Cell Biology, Istituto Dermopatico dell'Immacolata-IRCCS, Rome, Italy, [3] Department of Internal Medicine and Medical Specialties, "Sapienza" University of Rome, Rome, Italy, [4] NESMOS Department, "Sapienza" University of Rome, Rome, Italy

Vitiligo represents the most common cause of acquired skin, hair, and oral depigmentation, affecting 0.5–1% of the population worldwide. It is clinically characterized by the appearance of disfiguring circumscribed skin macules following melanocyte destruction by autoreactive cytotoxic T lymphocytes. Patients affected by vitiligo usually show a poorer quality of life and are more likely to suffer from depressive symptoms, particularly evident in dark-skinned individuals. Although vitiligo is a non-fatal disease, exposure of affected skin to UV light increases the chance of skin irritation and predisposes to skin cancer. In addition, vitiligo has been associated with other rare systemic disorders due to the presence of melanocytes in other body districts, such as in eyes, auditory, nervous, and cardiac tissues, where melanocytes are thought to have roles different from that played in the skin. Several pathogenetic models have been proposed to explain vitiligo onset and progression, but clinical and experimental findings point mainly to the autoimmune hypothesis as the most qualified one. In this context, it is of relevance the strong association of vitiligo with other autoimmune diseases, in particular with autoimmune thyroid disorders, such as Hashimoto thyroiditis and Graves' disease. In this review, after a brief overview of vitiligo and its pathogenesis, we will describe the clinical association between vitiligo and autoimmune thyroid disorders and discuss the possible underlying molecular mechanism(s).

Keywords: vitiligo, autoimmune thyroid diseases, tyrosinase, TSH receptor, thyroglobulin, reactive oxygen species, $CD8^+$ T cells, autoimmune polyendocrine syndromes

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Alessandro Antonelli, University of Pisa, Italy

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Ilaria Ruffilli, University of Pisa, Italy
Silvia Martina Ferrari, University of Pisa, Italy
Salvatore Benvenga, University of Messina, Italy
Flavia Di Bari, Policlinico di Messina, Italy

****Correspondence:***
Salvatore Ulisse
salvatore.ulisse@uniroma1.it

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VITILIGO: AN OVERVIEW

Vitiligo represents the most common cause of acquired skin, hair and oral depigmentation, and often occurs as an inherited disease (1). Clinically, it is characterized by the progressive loss of melanocytes causing the appearance of well-circumscribed milky/white cutaneous macules. Histologically, skin lesions show basal hypopigmentation and increased dermal inflammation relative to perilesional normal skin, with complete or near-complete loss of melanocytes at the basal epidermal layer (2). Following the Vitiligo Global Issues Consensus Conference in 2011, the disease has been categorized based on clinical parameters into: segmental vitiligo (SV), non-segmental vitiligo (NSV), and mixed vitiligo (MV) (1). SV is characterized by a unilateral distribution of the macules and is less common compared with the NSV, which shows symmetrical and bilateral white patches (3). NSV includes different clinical vitiligo subtypes, namely, acrofacial, generalized, mucosal, and universal vitiligo. NSV may be initially classified as acrofacial and, over time, be reclassified as generalized or universal

vitiligo. On the other hand, MV includes the combination of an initial SV followed by the occurrence, after several months or years, of bilateral NSV patches (1, 4).

The prevalence of vitiligo has been estimated to be 0.5–1% of the world population. However, it can vary from country to country. In fact, the prevalence recorded in Denmark is 0.38%, whereas in India it is up to 8.8% (1, 5, 6). Vitiligo can arise at any age, even if about 50% of cases are diagnosed before the age of 20, and both sexes are equally affected (1, 6).

Due to its disfiguring effects, vitiligo may have a detrimental impact on patient's quality of life (QoL) and mental health (7–9). A recent review of studies published over the last two decades indicates that women show more QoL impairment than men, married women more than singles, young patients more than elderly ones, and dark-skinned people more than white people (7, 8). Moreover, a recent meta-analysis demonstrated that vitiligo patients were significantly more likely to suffer from depression (9). Although vitiligo is a non-fatal disease, exposure of affected skin to UV light increases the chance of skin irritation and cancer (10). Furthermore, vitiligo has been associated with other rare systemic disorders, including the Vogt–Koyanagi–Harada, the Kabuki, and mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes (MELAS) syndromes due to the presence of melanocytes in other parts of the body, such as in eyes, auditory, nervous, and cardiac tissues, where melanocytes are thought to have different roles from that played in the skin (11). In particular, the Vogt–Koyanagi–Harada disease is an autoimmune multisystemic disorder branded by granulomatous panuveitis with exudative retinal detachments, neurologic and hearing manifestations, and vitiligo. The Kabuki syndrome manifests with abnormalities in multiple organ systems and is characterized by distinctive facial features, including arched eyebrows, long eyelashes, long openings of the eyelids with the everted lower lids, and large protruding earlobes. It usually associates with autoimmune diseases such as idiopathic thrombocytopenic purpura, hemolytic anemia, thyroiditis, and vitiligo. The MELAS syndrome is a mitochondrial disorder due to mutations of the mitochondrial genome. The typical presentation of patients with MELAS syndrome is described by the name of the disorder. Additional features are seizures, diabetes mellitus, hearing loss, cardiac disease, short stature, endocrinopathies, neuropsychiatric dysfunctions and skin alterations including hypertrichosis, eczema, and vitiligo.

PATHOGENESIS

Although several hypotheses have been put forward to explain vitiligo ethiopathogenesis, the autoimmune theory is the most accredited one, being sustained by several epidemiological, clinical, and experimental findings (4, 9, 11–17). These studies indicate that melanocyte defects drive vitiligo pathogenesis by triggering, in susceptible individuals, an autoimmune response that leads to melanocyte destruction (11). Several exogenous and endogenous stimuli have been linked to the onset of the disease. The exogenous factors include ultraviolet irradiations, trauma (Koebner phenomenon), stress, major infections, malignancies, neural abnormalities, vaccinations, pregnancy, calcium imbalance, certain drugs, hormones, and exposure to cytotoxic compounds. Among the endogenous factors are melanin synthesis, cellular metabolism, proliferation, differentiation, apoptosis, and immune reactions (11, 14, 18–20). All of these are thought to induce oxidative stress in melanocytes, as indicated by the high levels of reactive oxygen species (ROS), mainly hydrogen peroxide and peroxinitrite, found in lesional skin (11, 14, 18–20). The ROS increase may also result from compromised antioxidant responses with local and/or systemic imbalance of the antioxidant systems (11, 14, 18–20). For example, the superoxide dismutase is present at higher levels in perilesional skin and patient's sera (17, 20), whereas the level of the antioxidant enzyme catalase was found reduced in the vitiliginous skin compared with normal skin (20). The important role played by the antioxidant system in the pathogenesis of vitiligo is further corroborated by a recent study showing the association between a single nucleotide polymorphism of the nuclear factor, erythroid 2 like 2 (*NRF2*) gene and vitiligo (19, 21). The transcription factor Nrf2 regulates genes containing the antioxidant response elements (AREs) in their promoters and encoding proteins that protect against oxidative damage triggered by injury and inflammation. In addition, it has been shown that Nfr2-ARE/heme oxygenase-1 pathway is functionally deficient in the disease-free epidermis of patients with vitiligo (22). This is in agreement with very recent findings showing the ability of simvastatin to protect human melanocytes from H_2O_2-induced oxidative stress by activating Nrf2 (23). Finally, reduced levels of non-enzymatic antioxidants such as beta-carotene, ubiquinone, vitamins E and C, ferritin, and metallothionein may contribute to the increased amount of ROS observed in vitiliginous melanocytes (19).

Oxidative stress may affect the structure and functions of the endoplasmic reticulum (ER), which act as a cellular stress sensor. Dilation of the ER is a hallmark of melanocytes at the periphery of vitiligo lesions, and the disruption of redox reactions, critical for proper protein folding, causes the accumulation of immature proteins and misfolded peptides leading to the activation of the unfolded protein response (UPR) (24, 25). The latter, under sustained cellular stress, promotes autoimmune responses *via* apoptotic cascades (19). Actually, exposure to chemical triggers of vitiligo was shown to induce oxidative stress and to promote UPR activation in melanocytes (26). The importance of the UPR in the pathogenesis of vitiligo is further corroborated by several lines of experimental evidence, which identified the X-box binding protein 1 (*XBP1*) gene, encoding a transcription factor mediating UPR activation, as a susceptibility locus for generalized vitiligo (27–30). The UPR induces also the expression of cytokines, such as IL-6, IL-8, IL-11, and tumor necrosis factor, and can attract cells of the innate immune system to the skin of vitiligo patients, as documented by the aberrant activation of natural killer and dendritic cells (DCs) in lesional skin (11). More recently, a role for calreticulin (CRT), an ER protein regulating intracellular Ca^{2+}, has been proposed in the progression of vitiligo (19). In particular, a redistribution of CRT from the ER lumen to the plasma membrane of melanocytes takes place under oxidative stress (19). Surface CRT is thought to direct the contact of stressed melanocytes with DCs, eliciting downstream immune responses and melanocyte apoptosis. The latter provides

abundant antigenic peptides to the antigen-presenting cells leading to the activation of T cells, thus promoting autoimmunity. In this context, it is also worth to consider that the increased ROS levels are thought to modify tyrosinase (TYR) and other melanogenic proteins into neoantigens (11). Indeed, patients affected by vitiligo show circulating autoantibodies directed toward specific melanocyte antigens such as TYR, tyrosinase-related protein-1 (TRP-1), TRP-2, Pmel17 (or gp100), and type 1 membrane receptor for melanin-concentrating hormone, whose serum level correlates with the disease severity (11, 31–36). In early lesions, $CD8^+$ cytotoxic T lymphocytes have been found close to melanocytes, and a perivascular lymphocytic infiltrate could be appreciated at the expanding edge of active skin lesions (37). In addition, the concentration of melanocyte-specific $CD8^+$ T cells is higher in the blood of patients affected by vitiligo and correlates with disease activity (11, 31, 38). Furthermore, interferon-γ (IFN-γ) has been shown to play a central role in vitiligo progression through the release of several chemokines, such as CXCL9, 10, and 11 (17, 39). It has been also suggested that IFN-γ could play a direct role in vitiligo pathogenesis following the observation that the IFN-γ derived from cytotoxic T cells could itself cause apoptosis in melanocytes (40). This is in agreement with recent studies showing that human vitiligo as well as a mouse model of vitiligo reflects an IFN-γ-specific Th1 immune response in the skin that involves IFN-γ-dependent chemokines (41–44).

Recent findings indicate the participation in this process of TH17 cells, identified in the lesional skin of vitiligo patients (45, 46). The TH17 cells, by releasing interleukin-17, may induce in activated immune cells secretion of proinflammatory cytokines, which in turn recruit and activate mononuclear lymphocytes, strongly involved in disease progression (46). Finally, regulatory T cells (Treg), which are in charge to maintain peripheral tolerance through the suppression of self-reactive T cells, appear reduced in number and functionally flawed in lesional skin of patients affected by vitiligo (47).

A number of studies have shown that the uptake by keratinocytes of the melanocyte released melanosomes take place through phagocytic ingestion in a receptor-mediated process, involving the protease-activated receptor-2 and keratinocyte growth factor receptor/fibroblast growth factor receptor 2b (KGFR/FGFR2b) (48–50). A recent work reported a decreased expression of KGF/FGF7 and its receptor in pathological hypopigmented skin, which may contribute to the formation of the classical milky macules of vitiligo (50).

Finally, it is worth to mention that a number of genome-wide association and genetic linkage studies identified more than 30 different genes related to an increased risk of vitiligo, the majority of which are immune genes implicated in both the innate and the adaptive immune responses (4, 9, 11, 13).

ASSOCIATION WITH AUTOIMMUNE THYROID DISEASES (AITD)

Besides the abovementioned involvement of the immune system in vitiligo pathogenesis, epidemiological evidence further corroborates the autoimmune genesis of vitiligo. In particular, vitiligo is present within the autoimmune polyendocrine syndromes (51), and it is more frequently encountered in family members of patients affected by autoimmune diseases, such as inflammatory bowel disease, psoriasis, rheumatoid arthritis, type 1 diabetes, systemic lupus erythematosus, pernicious anemia, and AITD (31, 52–69). The latter, as outlined in several studies performed over the last decades, represent the most frequent autoimmune disorders associated with vitiligo (54, 58, 66–73). A recent meta-analysis, performed on 48 articles published between 1968 and 2012, showed that in patients affected by vitiligo the prevalence of AITD was 14.3%, while positivity to thyroid-specific antibodies [i.e., anti-thyroglobulin (Tg), anti-thyroid peroxidase, and anti-thyrotropin receptor (TSHR)] was found in 20.8% of them (74). Moreover, the presence of anti-thyroid hormones antibodies in the serum of patients affected by vitiligo was detected in 77 out of 79 vitiligo patients analyzed, suggesting a possible pathogenetic role (70, 75). *Vice versa*, the prevalence of vitiligo among AITD patients has been reported to vary from 2.7 to 7% (66, 67, 76, 77). It is also worth to note that the risk of thyroid disease in vitiligo patients increases with age (71, 74). All together, these findings have led to the recommendation of screening patients affected by vitiligo for thyroid diseases and thyroid autoantibodies, in an effort to detect undiagnosed thyroid diseases or to assess the risk of future onset (74, 78).

MOLECULAR MECHANISMS UNDERLYING VITILIGO AND THYROID AUTOIMMUNE DISEASE ASSOCIATION

The reported association of vitiligo with AITD suggests the presence of shared heritable susceptibility genes (79–87). Thirty-seven susceptibility genes have been identified for vitiligo disease and more than 15 for AITD (79–87). Genome-wide linkage analysis and candidate gene association studies identified nine loci potentially involved in both AITD and vitiligo (79–81). Among these, there are organ-specific genes such as those coding for TYR, Tg, and TSHR (81–85). In addition, an autoimmunity susceptibility locus (AIS1) was identified by genome-wide linkage analysis on chromosome 1 in families characterized by vitiligo and Hashimoto's thyroiditis (HT) (86–88). Among the 27 genes mapping to the AIS1 locus, the forkhead transcription factor D3 appears to be the most plausible responsible for the concomitant occurrence of vitiligo and AITD (86, 89). In addition, a single nucleotide polymorphism of the *PTPN22* gene, encoding a lymphoid specific phosphatase, is shared among patients with vitiligo and AITD (79). These findings suggest that the association observed between vitiligo and AITD could be explained, at least in part, by the sharing of a subset of susceptibility genes.

Of interest are the recently reported observations showing melanocyte-specific antigen expression in thyroid tissues of patients with HT, as well as in thyroid tissues of healthy individuals (88). In particular, thyroid tissues from HT patients without vitiligo, and normal thyroid tissues, were both negative for the expression

of NKI/beteb, Pmel17, TRP-1, HMB-45, and S100, whereas they were positive for the expression of TRP-2, lysosome-associated membrane protein 1 (LAMP1), and CD69. Interestingly, TYR was only detected in thyroid from HT patients. Moreover, levels of LAMP1 and CD69 were higher in thyroid with HT compared with normal thyroid (90). The differences in type and amount of melanocyte antigens observed in the thyroid of HT patients may provide the immunological basis for secondary vitiligo associated with HT. *Vice versa*, different skin cell types, including keratinocytes, dermal fibroblasts, and melanocytes, have been shown to express functional TSHR and other thyroid-specific antigens including Tg, thyroperoxidase, and natrium/iodide symporter (91, 92). Thus, it may be speculated that in vitiligo patients the activation of the immune system against these antigens expressed in vitiliginous melanocytes may cause a secondary AITD.

CONCLUSION

Knowledge regarding the pathogenesis of vitiligo has considerably increased over the last decades starting to clarify the molecular mechanisms underlying disease etiology and progression, as well as the association with other autoimmune disorders. Several susceptibility genes have been identified in both vitiligo and AITD patients that, along with the identification of shared antigens between melanocytes and thyrocytes, may contribute to explain the observed association between AITD and vitiligo.

AUTHOR CONTRIBUTIONS

All the authors contributed to the first draft of the article and its revision and approved its final version.

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Thyroid Autoimmunity and Lichen

Fabrizio Guarneri[1], Roberta Giuffrida[1], Flavia Di Bari[2], Serafinella Patrizia Cannavò[1] and Salvatore Benvenga[2,3,4]*

[1] Department of Clinical and Experimental Medicine – Dermatology, University of Messina, Messina, Italy, [2] Department of Clinical and Experimental Medicine – Endocrinology, University of Messina, Messina, Italy, [3] Master Program on Childhood, Adolescent and Women's Endocrine Health, University of Messina, Messina, Italy, [4] Interdepartmental Program of Molecular & Clinical Endocrinology and Women's Endocrine Health, University Hospital Policlinico "G. Martino", Messina, Italy

Lichen planus (LP) and lichen sclerosus (LS) are cutaneous-mucous diseases with uncertain epidemiology. Current data, which are likely to be underestimated, suggest a prevalence in the general population of 0.1–4% for cutaneous LP, 1.27–2.0% for oral LP, and 0.1–3.3% for LS. While etiology of lichen is still unknown, clinical and histological evidence show an (auto)immune pathogenesis. Association of lichen with autoimmune thyroid disease (AITD) has been investigated in few studies. This association appears better defined in the case of LS, while is more controversial for LP. In both situations, the frequency of the association is higher in females. We review the available literature on the correlation between the different types of lichen and AITD, and the literature on the genetic risk factors which are shared by both conditions. Such data suggest that a common pathogenic mechanism could be the cause for co-occurrence of lichen and AITD, at least in some patients. Additionally, analyzing literature data and in continuity with our previous work on other autoimmune diseases, we suggest that molecular mimicry could trigger both diseases, and thus explain their co-occurrence.

Keywords: autoimmune thyroid disease, oral lichen planus, mucous lichen planus, cutaneous lichen planus, lichen sclerosus, human leukocyte antigen, infections, molecular mimicry

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****Correspondence:***
Fabrizio Guarneri
f.guarneri@tiscali.it

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INTRODUCTION

Lichen planus (LP) is a cutaneous-mucous disease characterized by small papules and pruritus. Histologically, LP is characterized by hyperkeratosis, hypergranulosis, acanthosis with formation of colloid bodies (Civatte or Sabouraud bodies), vacuolar degeneration of the basal epidermal cell layer, "saw-tooth" appearance of the rete pegs, enlarged and deformed dermal papillae with infiltration of lymphocytes and histiocytes in a "band-like" pattern in contact with, and sometimes invading, the basal epidermal cell layer (1). Because of clinical similarity, over the years, several dermatological conditions were defined as "lichen" to eventually form the so-called lichenoid dermatoses, but with different specifications. For instance, lichen striatus is actually classified among spongiotic dermatoses, lichen amyloidosus among amyloidoses, and lichen aureus among mucinoses (1). A detailed discussion about lichenoid dermatoses is beyond the scope of this review. Only LP (cutaneous, mucosal and oral) and lichen sclerosus (LS)—also known as LS and atrophicus—for which autoimmunity has been postulated as a relevant part of the pathogenic mechanism, were reported to be associated with autoimmune thyroid disease (AITD).

Abbreviations: AITD, autoimmune thyroid disease; GD, Graves' disease; HT, Hashimoto's thyroiditis; LP, lichen planus; LS, lichen sclerosus; T4, thyroxine; Tg, thyroglobulin; TPO, thyroid peroxidase; TSH, thyroid stimulating hormone.

The epidemiology of LP and LS is not exactly defined. Current data, probably underestimated, suggest a prevalence in the general population of 0.1–4% for cutaneous LP (2), 1.27–2.0% for oral LP (3), and 0.1–3.3% for LS (4). Few authors investigated the association between these conditions and thyroid diseases and, even fewer, the possible common etiopathogenic mechanism(s).

We, herein, review the available literature on this topic. Moreover, in continuity with our previous studies on molecular mimicry as a trigger of autoimmune diseases, we suggest molecular mimicry as a potential pathogenic mechanism.

MATERIALS AND METHODS

We searched the PubMed database (https://ncbi.nlm.nih.gov/PubMed) using the search string "thyroid AND autoimm* AND lichen." The retrieved articles were revised, and only those discussing the association between lichen and AITD were selected. The reference lists of these articles were examined to find other relevant articles, which were also revised and included in this review if appropriate.

RESULTS

As of February 24, 2017, a PubMed search for "AITD" or "lichen" retrieved 14,864 and 15,311 articles, respectively. Conversely, a search for "thyroid AND autoimm* AND lichen," as described in Section "Material and Methods," yielded 40 articles of which 17 were selected as they were relevant for our review. Of these 17 articles, 15 analyzed the occurrence of AITD in patients with lichen (**Table 1**) and 2 analyzed the occurrence of lichen in patients with AITD (**Table 2**).

The first paper which suggested that LS "may be related to or caused by an autoimmune process" and highlighted the frequent association with thyroid autoimmunity was published in 1974 (5). In 26 patients (25 females and one male) with LS and 443 control subjects without autoimmune diseases, the authors evaluated the presence of antibodies to thyroglobulin (Tg), thyroid cytoplasm, gastric parietal cells, and type I intrinsic factor. Almost half of the female patients were positive for antithyroid cytoplasm antibodies [10/25 (40%), $p < 0.001$ vs controls] or anti-gastric parietal cells antibodies [11/25 (44%), $p < 0.001$ vs controls]; other tests were negative or not different from controls. Eight patients with antithyroid cytoplasm antibodies had subclinical thyroiditis (5).

The topic was brought again to attention many years later, in a case report of a 65-year-old woman with coexisting LS, AITD, morphea, and insulin-dependent diabetes mellitus (6). Next, a comment (7) to a review article (8) provocatively defined LS "a cutaneous manifestation of thyroid disease" (7). While this statement appears excessive in the light of modern knowledge, it is suggestive of the increase, started in the early 1990s, of awareness and interest concerning the possible connection between lichen and AITD (9–11). Larger studies, needed to define the epidemiological relevance of the association, have been performed only relatively recently.

LS and AITD

The largest, yet retrospective, study available on LS and AITD is on 532 patients with LS, predominantly adults and females ($n = 500$ and 396, respectively), who were visited in a German University hospital during 12 years (12). All patients were examined for cutaneous and extracutaneous autoimmune diseases. Tests included complete blood cell count, routine blood chemistry testing, complement components 3 and 4, C-reactive protein, and a panel of serological analyses for autoimmunity. This panel included antinuclear antibodies, extractable nuclear antibodies, rheumatoid factor, anti-cyclic citrullinated peptide antibodies, circulating immune complexes, and antibodies to thyroid peroxidase (TPO) and Tg. One or more autoimmune diseases were found in 82 patients (15.4%), with a significantly ($p < 0.0001$) different frequency among women ($n = 75$, 18.9%) and men ($n = 7$, 5.1%). AITD [Hashimoto's thyroiditis (HT) or Graves' disease (GD)] was the condition most often associated with LS, with a total of 65 cases (12.2%), again prevalently among females [$n = 60$ (15.2%), $p = 0.0002$ vs males]. Overall, cases of all other autoimmune diseases accounted for 3.3% of the studied sample.

Similar results were found by others. A case–control study in women was performed (13) on a smaller population (190 with adult-onset vulvar LS, 126 with adult-onset erosive vulvar LP, 922 age-matched controls). AITD was observed in 16.3% of patients with LS and 15% of patients with erosive LP compared to 7.9% in controls ($p < 0.001$ for both comparisons) (13). Kazandi et al. (14) retrospectively analyzed 82 women with vulvar LS and found 15 cases of thyroid disease (18.2%). A greater prevalence (29.9%) was reported in a retrospective evaluation of 211 patients visited in a 10-year period for vulvar LS (15). The percentage was higher among patients aged less than 55 years (33.8%) than among those aged 55 years or more (27.7%).

A different picture can be observed in studies on male LS. After the aforementioned article by Kreuter et al. (12), the largest and probably most complete study was published by Kantere et al. (16). The authors randomly chose 100 patients from 771 diagnosed with LS between 1997 and 2007 and re-evaluated their clinical condition. Such re-evaluation included clinical examination and laboratory tests, namely thyroid stimulating hormone (TSH), thyroxine (T4), antinuclear antibodies, and autoantibodies to extracellular matrix protein-1 (ECM-1), ECM-1 being the likely autoantigen of LS (17). Only five patients had mild abnormal thyroid function: low levels of T4 and raised levels of TSH (which is consistent with overt primary hypothyroidism) in two cases, normal T4 and raised TSH (which is consistent with subclinical primary hypothyroidism) in two other cases, normal T4 and decreased TSH in one (16). However, one paper (18) shows a different trend. Indeed, in a population of 60 women and 42 men, Hagedorn et al. (18) found that LS was associated with AITD in 39% of female and 12.5% of male patients.

LP (Oral, Mucous, Cutaneous) and AITD

The association between thyroid autoimmunity and LP, in its different subtypes, is more controversial, and the scarcity of papers does not allow clear conclusions. Soy et al. (19) evaluated the frequency of rheumatic and autoimmune diseases in 65

TABLE 1 | Studies reporting clinical and/or laboratory data about subjects affected by lichen who were found positive for AITD.

Reference, *Country*	Type of study and population	Main findings
Goolamali et al. (5), *England*	Cross-sectional study on 26 patients with **LS** (25 females, 1 males) and 443 controls without autoimmune diseases	10/25 (40%) of female patients were positive for antithyroid cytoplasm antibodies ($p < 0.001$ vs controls); 8 of these 10 patients had subclinical thyroiditis
Tremaine et al. (6), *Canada*	Case report	Report on a 65-year-old woman simultaneously affected by **LS**, AITD, morphea, and insulin-dependent diabetes mellitus
Kreuter et al. (12), *Germany*	Retrospective prevalence study on 532 patients affected by **LS** (396 females, 136 males)	AITD was associated with **LS** in 65 cases (12.2% of patients), prevalently among females [$n = 60$ (15.2%), $p = 0.0002$ vs males]
Cooper et al. (13), *England*	Case–control study on 190 women with adult-onset vulvar **LS**, 126 women with adult-onset erosive vulvar **LP**, 922 age-matched control women	AITD was observed in 16.3% of patients with **LS** and 15% of patients with erosive **LP** vs 7.9% of controls ($p < 0.001$ for both comparisons)
Kazandi et al. (14), *Turkey*	Retrospective prevalence study on 82 women with vulvar **LS**	15 cases of thyroid disease were observed (18.2% of patients)
Birenbaum and Young (15), *USA*	Retrospective prevalence study on 211 women with vulvar **LS**	63 cases of AITD were observed (29.9% of patients). Prevalence of AITD was higher among patients aged less than 55 years [25/74 (33.8%)] than those aged 55 years or more [38/137 (27.7%)]
Kantere et al. (16), *Sweden*	Cross-sectional study on 100 patients with **LS**	No patients with thyroid disease, five with mild abnormality of thyroid function: low levels of T4 and raised levels of TSH in two cases, normal T4 and raised TSH in two other cases, normal T4 and decreased TSH in one
Hagedorn et al. (18), *Germany*	Cross-sectional study on 102 patients (60 females, 42 males) with **LS**	AITD was found in 39% of females and 12.5% of males
Ebrahimi et al. (20), *Sweden*	Cross-sectional study on 120 patients (89 females, 31 males) with mucosal **LP** and 87 age- and sex-matched healthy controls	AITD was found in 11/120 patients (9.2%)
Chang et al. (21), *Taiwan*	Cross-sectional study on 500 patients with desquamative gingivitis, 287 with erosive oral **LP** without desquamative gingivitis, and 100 healthy controls	455 patients with desquamative gingivitis were affected by erosive oral **LP**; 46.4% of them were positive for anti-Tg and 45.1% for antithyroid microsomal antibodies. The corresponding percentages were 27.5 and 30.3%, among patients with erosive **LP** but not gingivitis. For both groups of patients, differences in comparison with healthy controls were significant ($p < 0.001$). Overall, 210 patients were positive for at least one thyroid autoantibody, and TSH levels were normal in 84.3%, decreased in 6.7% and increased in 9% of them
Chang et al. (22), *Taiwan*	Cross-sectional study on 320 patients with oral **LP** (292 erosive, 28 non-erosive)	Anti-Tg and antithyroid microsomal antibodies were found in 21.3 and 24.4% of patients. TSH levels were normal in 85.8% of the 190 patients, positive for one or both thyroid autoantibodies, below normal in 4.2% and above normal in 10%
Carrozzo et al. (23), *Italy*	Cross-sectional study on 50 patients with oral **LP**	Antithyroid antibodies were found in 10% of patients
Lavaee and Majd (24), *Iran*	Retrospective prevalence study on 523 patients with oral **LP** (387 females, 136 males) and 523 age- and sex-matched healthy controls	Hypothyroid subjects were 35 among patients (6.7%) and 21 among controls (4%); this difference was not statistically significant
Azurdia et al. (31), *England*	Cross-sectional study on 58 males affected by **LS** and 602 healthy controls	*HLA-DR11*, *-DR12*, and *-DQ7* were significantly ($p \leq 0.05$) more frequent in patients, but no cases of AITD were found among them. One patient had a mild increase of serum T4 with normal TSH levels, another one had slightly lower than normal serum T4, with normal TSH. A third patient had positive antithyroid antibodies, but normal thyroid function
Aslanian et al. (32), *Brazil*	Cross-sectional study on three families (30 subjects in total) with familial **LS**	8 cases of **LS** were found among the 30 subjects visited; seven of these patients were positive for anti-TPO antibodies, but only four had clinical AITD. The *HLA-B*15-DRB1*04-DRB4** haplotype was associated with the co-occurrence of **LS** and thyroid autoimmunity

The type of lichen studied in each paper is written in boldface.
AITD, autoimmune thyroid disease; LP, lichen planus; LS, lichen sclerosus; T4, thyroxine; Tg, thyroglobulin; TPO, thyroid peroxidase; TSH, thyroid stimulating hormone; HLA, human leukocyte antigen.

patients (56 women and 9 men) with AITD. Oral LP was one of the less represented diseases, as it was found in only two patients (3.1%). Ebrahimi et al. (20) evaluated 120 patients with mucosal LP and 87 age- and sex-matched healthy controls for the presence of other diseases, with particular attention to autoimmune and thyroid diseases. They found a significantly high frequency of autoimmune diseases in general (28%) and AITD in particular (9.2%) among patients. These results, together with the observation that lichen was multifocal in 72% of women and 64% of men, led the authors to conclude that "LP with mucosal involvement

TABLE 2 | Studies reporting clinical and/or laboratory data about subjects affected by AITD who were found positive for lichen.

Reference, *country*	Type of study and population	Main findings
Soy et al. (19), *Turkey*	Cross-sectional study on 65 patients (56 females, 9 males) with AITD	Oral **LP** was found in two patients (3.1%)
Brănişteanu et al. (25), *Romania*	Retrospective prevalence study on 38 patients (36 Females, 2 males) with thyroid diseases (63% autoimmune thyroiditis, 26.3% polynodular goiter, 10.7% hypothyroidism)	**LP** was found in 18% of patients and was the second most frequent dermatological disorder after alopecia areata (22%)

The type of lichen studied in each paper is written in boldface.
AITD, autoimmune thyroid disease, LP, lichen planus.

should be considered and taken care of as a systemic disease" and to point out "the need for a multidisciplinary clinic to get optimal care and treatment" (20). Another paper concerning mucosal lichen, namely adult-onset erosive vulvar LP, is by Cooper et al. (13) (see above, Section "LS and AITD"). Further, interesting elements come from a recent paper (21). This paper (21) aimed to define the number of patients with desquamative gingivitis (a disease often associated with erosive oral LP) who were positive for anti-gastric parietal cells, anti-Tg, and antithyroid microsomal antibodies. They analyzed 500 patients with desquamative gingivitis, 287 with erosive oral LP but without desquamative gingivitis, and 100 healthy controls. Upon careful reevaluation, erosive oral LP was found in 455 patients of the first group: 46.4% of them were positive for anti-Tg and 45.1% for antithyroid microsomal antibodies. The percentages were 27.5 and 30.3%, respectively, among patients of the second group. Differences from controls were significant ($p < 0.001$) for both groups of patients. Overall, 210 patients were positive for at least one thyroid-related autoantibody, and TSH levels were normal in 84.3%, low in 6.7%, and raised in 9% of them (21). In a previous study (22), the same group had found a prevalence of 21.3 and 24.4% for anti-Tg and antithyroid microsomal antibodies, respectively, among 320 patients with oral LP (erosive in 292 cases, non-erosive in 28). In the same study, TSH levels were normal in 85.8% of the 190 patients positive for one or both thyroid-related autoantibodies, low in 4.2% and raised in 10% (22). Other authors had reported antithyroid antibodies in 10% of 50 patients with oral LP (23).

Lavaee and Majd (24) retrospectively evaluated the frequency of hypothyroidism in 523 patients with oral LP (387 females, 136 males) and in an equal number of age- and sex-matched healthy controls. They found statistically similar proportions (6.7 and 4%, respectively).

Finally, Brănişteanu et al. published data about the association between AITD and cutaneous LP (25). The study population included 38 patients (36 females, 2 males) with thyroid diseases (63% autoimmune thyroiditis, 26.3% multinodular goiter, 10.7% hypothyroidism), who accessed the Dermatovenereology Unit of a University hospital over 2 years. LP was the second most frequent dermatological disorder observed (18%) after alopecia areata (22%).

Genetic Risk Factors: Possible Role of Human Leukocyte Antigen (HLA)

The studies mentioned in the previous sections suggest that all subtypes of lichen, AITD, and also their association, are more frequent in females.

Given the autoimmune pathogenesis of both conditions, several authors analyzed the possibility of a link with specific alleles of the *HLA* genes. As well known, *HLA* genes generate the major histocompatibility complex (MHC) molecules, responsible for presentation of (auto)antigenic peptides to the immune system and activation of the consequent specific (auto)immune reaction.

Studies on the *HLA* haplotype of patients with lichen are few, not very recent, and often performed on small cohorts. Porter et al. (26) reported that cutaneous LP has been associated to *HLA-A3*, *-A5*, *-A28*, *-B16*, and *-Bw35*, mucosal LP to *HLA-A3* and *-A28*, oral LP to *HLA-B16*, *-DR1*, and *-DRw9*, erosive oral LP to *HLA-DR2*, *-DR3*, *-DR9*, *-B27*, and *-Bw57*, mixed oral LP to *HLA-B51* [for references, see Ref. (26)]. The studies reviewed had populations ranging from 10 to 82 patients, and had been published between 1976 and 1994. For LS, the most recent review (27) suggests a strong linkage to *HLA-DQ7*. In a subsequent case–control study (28), an increased frequency of *HLA-DRB1*12/DQB1*03* was found in 187 patients with vulvar LS.

A comparison with AITD-associated *HLA* alleles (29) shows some elements in common: *HLA-B16* confers increased risk for HT in Asians, *HLA-DR3* is linked to GD (in Caucasians) and HT, *HLA-DR9* is a risk factor for GD in Japanese and Chinese subjects and HT in Chinese patients only [for references, see Ref. (29)]. Among patients with stress-related GD, *HLA-A28* is significantly more frequent (at least 3-X) in those with exacerbations of hyperthyroidism compared with those with no exacerbations during treatment with antithyroid drugs, while *HLA-DR3* is almost 3-times more frequent in the whole group of patients with stress-related GD compared with healthy controls (30).

The above data could suggest a common genetic background of susceptibility for lichen and thyroid autoimmunity. However, we found only two studies that evaluated the *HLA* haplotypes of patients for which the association between lichen and AITD was explicitly investigated (31, 32). Azurdia et al. (31) analyzed 58 males with LS and 602 healthy controls, and showed a significantly ($p \leq 0.05$) higher frequency of *HLA-DR11*, *-DR12*, and *-DQ7* in patients. In detail, the frequencies of *HLA-DR11*, *-DR12*, and *-DQ7* were 22, 9, and 45% among patients and 13, 3, and 31% among controls, respectively. Abnormal thyroid function was observed in two cases: one patient had a mild increase of serum T4 with normal TSH levels, while another had slightly subnormal serum T4, and normal TSH. Positive antithyroid antibodies, but normal thyroid function, were found in a third patient (31). In the second paper, Aslanian et al. (32) examined three families, of 20, 8, and 2 members, respectively, with familial LS. Eight subjects with LS were found among the

30 visited, 7 of whom were positive for anti-TPO antibodies, but only 4 had a thyroid disease. The *HLA-B*15-DRB1*04-DRB4** haplotype was associated with the co-occurrence of LS and thyroid autoimmunity (32). HLA-*DRB1*04* was almost threefold more frequent in patients with stress-related GD compared with healthy controls (30).

Environmental Triggering Factors: Association with Infections and the Molecular Mimicry Hypothesis

Like most autoimmune diseases, the environmental triggers of LS and AITD are unknown, and also unknown is whether an etiopathogenic link between the two conditions exists.

We previously reported a woman who developed both LS and HT after infection by *Borrelia burgdorferi* (33). In that occasion, the chronological sequence and correlation between the pathological events led us to hypothesize that molecular mimicry between bacterial antigen(s) and human autoantigens could have been the pathogenic mechanism by which borreliosis had triggered both autoimmune diseases (33). According to the molecular mimicry hypothesis, structural similarity between microbial antigens and human autoantigens can turn a defensive immune reaction into an autoimmune reaction in genetically predisposed subjects (mainly because of specific *HLA* alleles). This model has been postulated, and in many cases demonstrated, as a possible explanation for the onset of autoimmunity (34–41).

Several studies on the possible role of molecular mimicry in the pathogenesis of autoimmune and allergic diseases were performed also by our group, with extensive use of bioinformatics tools (42–53). In detail, we searched for amino acid sequence homology between human protein autoantigens involved in specific autoimmune diseases and proteins from microbes that are clinically linked to such diseases. In many cases, we also searched the homologous segments of human and microbial proteins for binding motifs of MHC molecules derived from specific *HLA* alleles.

Following the hypothesis formulated in our case report (33), we aimed to identify the molecules most probably involved in triggering autoimmunity after *Borrelia* infection (42, 45). We found that human TSH-R has four segments homologous to proteins from *Borrelia* and five homologous to proteins from *Yersinia*, another bacterial species associated with AITD. In a subsequent study (45), we extended our work to include the other known thyroid autoantigens (TPO, Tg, sodium iodide symporter) and to search human and microbial proteins for the occurrence of peptide-binding motifs of *HLA-DR* molecules. Eleven additional homologies were found with proteins from *Borrelia* (2 with Tg, 3 with TPO, 6 with sodium iodide symporter) and 15 with proteins from *Yersinia* (2 with Tg, 2 with TPO, 11 with sodium iodide symporter). The number of binding motifs related to the different *HLA-DR* alleles agreed well with literature data, which suggest that AITD is associated with *HLA-DR3*, *-DR4*, *-DR5*, *-DR8*, and *-DR9*.

Concerning the association between *Borrelia* and lichen, in 1985, Asbrink wrote that "a *Borrelia* infection may result in lichen sclerosus et atrophicus-like reactions" (54), a claim that was subsequently supported by others (55–59). Although the debate remains open, a pathogenic link between borreliosis and lichen seems to exist in some cases (60). Our preliminary data (61) show that ECM-1, which is the autoantigen of LS (17), is homologous to BBG23 and methyl-accepting chemotaxis protein (mcp-3) of *B. burgdorferi*. All four thyroid autoantigens, ECM-1, and their corresponding homologous *Borrelia* proteins contain 4–32 copies of the binding motif related to *HLA-DQ7*, this allele conferring genetic susceptibility to both AITD (62) and LS (31).

Molecular mimicry appears as an interesting field of investigation, and might explain, at least in part, associations found in epidemiological studies and/or single case reports. In our experience, it gave a plausible explanation for the association between AITD and *Yersinia* infection (42, 45, 50), anti-tumor vaccination with NY-ESO-1 (51), or rickettsiosis (52).

The main other infectious agents that the literature has linked to AITD are Epstein–Barr virus (63), hepatitis C virus (64), parvovirus B19 (64), human herpesvirus-6 (65), and *Helicobacter pylori* (66). For lichen, association was reported with Epstein–Barr virus—also known as human herpesvirus 4 (67), hepatitis C virus (67, 68), human papillomavirus (67, 69), and human herpesvirus-7 (70), while correlation with *H. pylori* is controversial (71, 72).

CONCLUSION

The existence and nature of a connection between AITD and lichen are still unresolved issues. Echoing Braun-Falco et al. (1), the etiology of lichen is currently "a mistery." Molecular mimicry is a likely mechanism, especially considering the advantage of providing an explanation for the occurrence of the association in patients with given *HLA* genotypes. However, molecular mimicry alone may not explain entirely the complex pathogenesis of the association, and other possibilities should be evaluated. Better awareness and attention to the association of lichen and AITD, and increased interdisciplinary collaboration, is desirable to define epidemiological magnitude and detailed clinical characteristics of the association, taking into account variables, such as ethnicity, socioeconomic issues, and environmental issues. Hopefully, better basic and clinical research will generate more effective care to patients with coexisting lichen and AITD.

AUTHOR CONTRIBUTIONS

SB and FG: substantial contributions to the conception or design of the work, drafting of the work, final approval of the version to be published, and agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. SPC, FDB, and RG: acquisition/analysis/interpretation of data for the work, critical revision for important intellectual content, final approval of the version to be published, and agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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MINI REVIEW
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Psoriasis, Psoriatic Arthritis, and Thyroid Autoimmunity

Ilaria Ruffilli [1], Francesca Ragusa[1], Salvatore Benvenga[2,3,4], Roberto Vita[2], Alessandro Antonelli [1], Poupak Fallahi[1] and Silvia Martina Ferrari[1]*

[1] Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy, [2] Department of Clinical and Experimental Medicine, University of Messina School of Medicine, Messina, Italy, [3] Master Program of Childhood, Adolescence and Women's Endocrine Health, University of Messina School of Medicine, Messina, Italy, [4] Interdepartmental Program of Molecular & Clinical Endocrinology, and Women's Endocrine Health, University Hospital, Messina, Italy

Psoriasis (PsO) is a chronic relapsing/remitting autoimmune skin disease, associated with an increased risk of other autoimmune disorders. Psoriatic arthritis (PsA) is a chronic inflammatory arthritis occurring approximately in 30% of PsO patients. Sporadic cases of association between PsO and autoimmune thyroid disorders (AITDs) have been reported. However, two different recent studies did not find any association between them. In patients with PsO and PsA, an association with AITD has been shown by most of the studies in adults, but not in the juvenile form. In PsA women and men, thyroid autoimmunity [positive antithyroid peroxidase (AbTPO) antibodies, hypoechoic thyroid pattern] and subclinical hypothyroidism were more prevalent than in the general population. An association has been shown also in patients with PsO, arthritis, and inflammatory bowel disease, who have more frequently AITD. A Th1 immune predominance has been shown in early PsO, and PsA, with high serum CXCL10 (Th1 prototype chemokine), overall in the presence of autoimmune thyroiditis. This Th1 immune predominance might be the immunopathogenetic base of the association of these disorders. A raised incidence of new cases of hypothyroidism, thyroid dysfunction, positive AbTPO, and appearance of a hypoechoic thyroid pattern in PsA patients, especially in women, has been shown recently, suggesting to evaluate AbTPO levels, thyroid function, and thyroid ultrasound, especially in PsA women. Thyroid function follow-up and suitable treatments should be performed regularly in PsA female patients at high risk (thyroid-stimulating hormone within the normal range but at the higher limit, positive AbTPO, hypoechoic, and small thyroid).

Keywords: psoriasis, psoriatic arthritis, autoimmune thyroiditis, hypothyroidism, CXCL10, AbTPO, anti-thyroglobulin antibodies

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Maria Brito, Mount Sinai Health System, United States
Tony Weetman, University of Sheffield, United Kingdom

****Correspondence:***
Ilaria Ruffilli
ilaria.ruffilli@gmail.com

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INTRODUCTION

Psoriasis (PsO) (1) affects about 2–4% of the population (2); it is a chronic relapsing/remitting autoimmune skin disease (1) and presents with itchy red, scaly patches, papules, and plaques, with different severity, from localized patches to general body coverage. PsO is classified in five types: plaque, guttate, inverse, pustular, and erythrodermic (3). These lesions are usually evident on the skin

Abbreviations: AITDs, autoimmune thyroid diseases; AT, autoimmune thyroiditis; AbTg, anti-thyroglobulin antibodies; AbTPO, antithyroid peroxidase antibodies; FT4, free thyroxine; IBD, inflammatory bowel disease; IFN, interferon; IL, interleukin; JIA, juvenile idiopathic arthritis; PsA, psoriatic arthritis; PsO, psoriasis; RA, rheumatoid arthritis; RF, rheumatoid factor; TD, thyroid dysfunction; TSH, thyroid-stimulating hormone.

of elbows and knees, and also on scalp, palms of hands, and soles of feet. Psoriatic nail dystrophy is usually present in fingernails and toenails and can be an isolated sign. A genetic predisposition is very important in the pathogenesis of PsO; however, environmental factors can activate the disease (1).

The skin epidermal layer grows rapidly in PsO (4), determining an abnormal production and an excess of skin cells (5), that are replaced in 3–5 days in PsO (while commonly every 28–30 days) (6). These events are probably induced by the premature keratinocytes maturation, induced by the inflammatory cascade in the dermis (7). The immune competent cells go from dermis to epidermis and release different inflammatory cytokines [interleukin (IL)-1β, interferon (IFN)-γ, tumor necrosis factor-α, chemokine (C-X-C motif) ligand (CXCL)10, IL-6, IL-22] (8). In PsO, DNA can stimulate the dendritic cells, to produce IFN-α. The secretion of such inflammatory cytokines leads to stimulate the proliferation of keratinocytes (8).

Psoriatic arthritis (PsA) is a chronic inflammatory arthritis that has a variable clinical presentation and occurs approximately in 30% of PsO patients (7, 9, 10). PsA typically affects the joints of the fingers and toes, and it is characterized by a painful inflammation of the joints and surrounding connective tissue. This process results in a sausage-shaped swelling of the fingers and toes called dactylitis (9). PsA can also affect the hips, spine (spondylitis), knees, and sacroiliac joint (sacroiliitis), and any other joint (11). Dermatologic manifestations of PsO appear before the manifestations of arthritis in about 75% of patients (10).

Psoriasis is associated with an increased risk of other autoimmune disorders like ulcerative colitis, Crohn's disease, and autoimmune thyroiditis (AT) too (12).

Here, we review the scientific literature about PsO, PsA, and the possible association with autoimmune thyroid disorders (AITDs).

PsO, PsA, AND AITD

Few case reports initially reported an association of PsO and Hashimoto's thyroiditis (13, 14) (**Table 1**). A first systematic study by Bianchi et al. (15) evaluated thyroid volume and function and the prevalence of anti-microsome and anti-thyroglobulin antibodies (AbTg) in 42 patients with PsA, versus 52 normal subjects, as controls. The average thyroid volume, measured at ultrasounds, was increased in comparison to controls. Patients with PsA had a raised prevalence of anti-microsome antibodies; thyroid involvement was confined to patients with active disease. These results suggested a significant thyroid involvement in PsA patients. However, the study was basically a retrospective study, and it did not specify the selection criteria of the patients (15).

A second study evaluated the prevalence of thyroid disorders in PsA patients, conducting a complete thyroid work-out in 80 PsA patients, versus control subjects extracted (1:5) from the general population (matched by age and gender), and 112 patients with rheumatoid arthrtitis (RA) (with similar iodine intake). PsA women had significantly more frequently a hypoechoic thyroid pattern, antithyroid peroxidase antibodies (AbTPO), and subclinical hypothyroidism than control women, with a frequency comparable to that in RA patients (hypoechoic thyroid 31, 16, and 36%; positive AbTPO titer 28, 12, and 31%; subclinical hypothyroidism 25, 8, and 12%, respectively). PsA and RA men showed more frequently hypoechoic thyroid pattern and positive AbTPO than control subjects (hypoechoic thyroid 16, 10, and 3%; positive AbTPO titer 14, 5, and 2%, respectively). PsA patients with subclinical hypothyroidism had a longer disease duration (years; 19 ± 15 versus 11 ± 8, $p = 0.03$) and polyarticular involvement ($p \leq 0.05$) than euthyroid PsA patients. Therefore, a significantly higher prevalence of thyroid autoimmunity (positive AbTPO, hypoechoic thyroid pattern) in PsA men and women, and of subclinical hypothyroidism in PsA women, than in the general population were evidenced (12). Conversely, a subsequent study investigated the frequency of rheumatic diseases in 65 patients (56 F, 9 M), suffering from AITD; antinuclear antibody and rheumatoid factor levels were also measured. Various rheumatic disorders were detected in 40 (62%) of patients with AITD: the most frequent were fibromyalgia, osteoarthritis, keratoconjunctivitis sicca, and xerostomia. Autoimmune diseases were detected in 10 patients with AITD, and among them also PsO and PsA (19). A further study (20) evaluated the frequency of AITD in 80 children with juvenile idiopathic arthritis (JIA) (27

TABLE 1 | Prevalence of thyroid autoimmunity in psoriasis (PsO), or psoriatic arthritis (PsA) patients, versus controls, in the studies that have an internal control group.

Reference	PsO patients (*n*)	Autoimmune thyroid disorder (AITD)% in PsO patients	Controls (*n*)	AITD% in controls	*P*
Antonelli et al. (12)	80 with PsA	12/36 of F patients (33%); 11/44 of M patients (25%)	112 patients with rheumatoid arthritis; 400 control subjects	33/180 of F controls (18%); 10/220 of M controls (5%)	0.0001
Bianchi et al. (15)	42 with PsA	AbTg prevalence 5%; anti-microsome antibodies prevalence 14%	52	AbTg prevalence 3%; anti-microsome antibodies prevalence 0%	<0.05
Gul et al. (16)	105	6 patients had increased AbTPO (6%); 8 patients had increased AbTg (8%); 3 patients had both increased AbTPO and AbTg (3%)	96 with tinea pedis	AbTPO levels were increased in 6 subjects (6%), AbTg levels were increased in 11 subjects (11%) and both of them were increased in 6 subjects (6%)	NS
Vassilatou et al. (17)	114 (30 of them with PsA)	Prevalence of autoimmune thyroiditis (AT) 20.2%	286	Prevalence of AT 19.6%	NS
Fallahi et al. (18)	97 with PsA	34% thyroid autoimmunity	97	15% thyroid autoimmunity	0.002

AbTg, anti-thyroglobulin antibodies; AbTPO, anti-thyroperoxidase antibodies; F, females; M, males; NS, not significant.

oligoarticular, 26 polyarticular, 17 enthesitis-related, 6 systemic, and 4 PsA), versus 81 healthy control subjects, matched by age and gender. AITD were found in four patients in the JIA group (5%). No significant difference between the study and control groups was observed in the frequency of circulating antithyroid antibodies, or AT, suggesting that in JIA there is no association with AITD (20).

A further study evaluated thyroid autoimmunity in 105 patients with PsO (without PsA), versus 96 sex- and age-matching controls (with tinea pedis). The levels of free thyroxine (FT4) resulted significantly increased in the PsO group; however, AbTPO and AbTg levels were not significantly different between the two groups. The study showed that the serum FT4 levels can increase in psoriatic patients. However, thyroid-stimulating hormone (TSH), FT4, or FT3 were not reported. Furthermore, an increase of FT4 should be related to TSH decreased levels, however any correlation was reported (16).

The association between PsO and inflammatory bowel disease (IBD) has been previously reported, even if potential associated comorbidities are not clear. A study (21) examined comorbidities in 146 patients diagnosed with both PsO and IBD, in comparison with those diagnosed with PsO-only (146, matched by gender, ethnicity, and age). Patients with both PsO and IBD (versus PsO-only) had significantly higher rates of hepatitis (6.2 versus 0.7%), AT (6.8 versus 2.1%), and diabetes (26.77 versus 11.0%), and 60 (41.1%) were diagnosed with seronegative arthritis, suggesting that patients with both PsO and IBD have more frequently AITD and arthritis (21).

The prevalence of 12 autoimmune diseases was also evaluated in 25,885 people extracted from the general population in Sardinia (22). A high prevalence was observed for RA, ulcerative colitis, Crohn's disease, type 1 diabetes, systemic lupus erythematosus, celiac disease, myasthenia gravis, systemic sclerosis, multiple sclerosis, Sjogren's syndrome, PsO/PsA (939 cases), and AT (2,619 cases). The statistical analysis of the comorbidity of autoimmune diseases shows that the number of people with more than one autoimmune disease was significantly higher than the expected number, both in women and men (22).

Another study (17) evaluated prospectively 114 PsO patients with disease duration of 5–38 years, 30 of them with PsA, in comparison with 286 age- and body mass index-matched subjects. No difference in the prevalence of AT between PsO patients and controls (20.2 versus 19.6%) was present. The prevalence of AT in male and female PsO patients was similar (9.6 and 10.5%, respectively) unlike the increased, as expected, prevalence in female versus male controls (14.7 versus 4.9%). Detected cases with hypothyroidism due to AT were similar in PsO patients and controls (7.9 and 7.0%, respectively). However, the number of patients with PsA was low (23) and not sufficient to a reliable evaluation of AITD in these last patients (17).

Conversely, a subsequent study evaluated prospectively the prevalence of other autoimmune disorders in outpatient clinic in 3,069 consecutive patients with diagnosed chronic AT, with respect to two age- and sex-matched control groups: (a) a control group of 1,023 subjects, extracted from a random sample of the general population without thyroid disorders and (b) 1,023 patients with non-toxic multinodular goiter drawn by the same random sample of the general population, with similar iodine intake. The results of our study demonstrated a significant increase of the prevalence of PsA in AT patients (24).

A more recent study (18) aimed to assess the incidence of new cases of clinical and subclinical thyroid dysfunction (TD) in a broad group of PsA patients versus a control group, matched by age and gender with a similar iodine intake. PsA patients with TD were excluded first, and new cases of thyroid disorders were evaluated in 97 PsA patients and 97 matched controls (median follow-up of 74 months in PsA versus 92 in controls). A raised rate of new cases of hypothyroidism, TD, positive AbTPO, and appearance of a small hypoechoic thyroid pattern in PsA, especially in female gender, compared to controls has been evidenced. Risk factors in female gender for the development of TD were TSH within the normal range but at the higher limit, positive AbTPO, and small thyroid volume (18).

Interferon-γ and Th1 cytokines/chemokines are involved in the pathogenesis of PsO. Activated T cells and HLA-DR keratinocytes have been shown in active plaques (25). It has been shown that CXCL10, the Th1 prototype chemokine, and its receptor (CXCR)3 are present in keratinocytes and in the dermal infiltrate derived from active psoriatic plaques and that effective treatment of active plaques decreased the expression of CXCL10. Elevated circulating CXCL10 has been shown in PsO patients (25–28). The cellular infiltrate in acute plaques is constituted by 5–8% CD3(−)CD56(+) NK cells, as indicated by immunohistochemical techniques, especially localized in the mid and papillary dermis. NK lymphocyte migration toward CXCL10 is involved in the pathogenesis of PsO (27).

CXCL10 is a determinant chemoattractant for neutrophils, and an elevated infiltration and microabscess formation by neutrophils is a characteristic PsO feature. Different papers have shown a critical pathogenic role of neutrophils in PsO, particularly in the first phases, leading to hypothesize that blocking neutrophil function could have therapeutic effectiveness in this disease (23, 29, 30).

Also, in PsA patients, high levels of CXCL10 are observed in synovial fluid, and in circulation. Th1 cells immune predominance has been also shown at the beginning of the disease, with a subsequent later decline in long-lasting PsO or PsA, suggesting a shift from Th1 to Th2 immune response in long duration diseases (31–33).

Also, AITD are Th1 immune-mediated autoimmune disorders in which Th1 lymphocytes, IFN-γ, and IFN-γ dependent chemokines (CXCL9, CXCL10, CXCL11) play an important role (34, 35).

Serum levels of CXCL10 (the Th1 prototype chemokine) and CCL2 (the Th2 prototype chemokine) were measured in 37 patients with PsA without AT (PsA) and 28 with AT (PsA + AT), and in gender- and age-matched controls. The results of the study demonstrated higher circulating CXCL10 and CCL2 in PsA patients than in control subjects. Furthermore, serum CXCL10 (but not CCL2) levels in PsA patients were significantly higher in the presence of AT (36). These data suggested that a Th1 immune predominace, both in PsA such as in AT, might be the immunopathogenetic base of the association of these diseases.

CONCLUSION

Psoriasis is associated with an increased risk of other autoimmune disorders like ulcerative colitis, Crohn's disease, and celiac disease (37). Sporadic cases of association of PsO and AITD have been reported. However, two different recent studies did not find any association between PsO and AITD.

Psoriatic arthritis is a chronic inflammatory arthritis that occurs approximately in 30% of PsO patients. In patients with PsO and PsA, an association with AITD has been shown by most of the studies in adults, but not in the juvenile form. In PsA women and men, thyroid autoimmunity (positive AbTPO antibodies, hypoechoic thyroid pattern) and subclinical hypothyroidism were more prevalent than in the general population. An association has been shown also in patients with PsO, arthritis, and IBD who have more frequently AITD.

A Th1 immune predominance has been shown in early PsO, and PsA, such as in AT, with high circulating levels of the Th1 prototype chemokine CXCL10 overall in the presence of the association with AT. These data suggest that this Th1 immune predominance might be the immunopathogenetic base of the association of these disorders.

A very recent longitudinal study in PsA patients has shown a raised incidence of new cases of hypothyroidism, TD, positive AbTPO, and appearance of a small and hypoechoic thyroid in PsA, especially in female gender, compared to controls. Risk factors in female gender for the development of TD are TSH within the normal range but at the higher limit, positive AbTPO, and small thyroid volume, suggesting to evaluate AbTPO levels, thyroid function, and thyroid ultrasound, especially in PsA women. Thyroid function follow-up and suitable treatments should be performed regularly in PsA female patients at high risk TSH within the normal range but at the higher limit, positive AbTPO, hypoechoic, and small thyroid.

However, studies in larger number of patients are required to evaluate if routine thyroid screening could be beneficial for PsO patients.

AUTHOR CONTRIBUTIONS

IR, FR, SB, RV, AA, PF, and SMF gave substantial contribution in the conception and design of the work, and in writing the paper; gave the final approval of the version to be published; agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. AA and SB revised it critically for important intellectual content.

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Autoimmune Thyroiditis and Myasthenia Gravis

*Angela Lopomo[1] and Sonia Berrih-Aknin[2,3,4]**

[1] Department of Translational Research and New Technologies in Medicine and Surgery, Division of Medical Genetics, University of Pisa, Pisa, Italy, [2] Sorbonne Universités, UPMC Univ Paris 06, Paris, France, [3] INSERM U974, Paris, France, [4] AIM, Institute of Myology, Paris, France

Autoimmune diseases (AIDs) are the result of specific immune responses directed against structures of the self. In normal conditions, the molecules recognized as "self" are tolerated by immune system, but when the self-tolerance is lost, the immune system could react against molecules from the body, causing the loss of self-tolerance, and subsequently the onset of AID that differs for organ target and etiology. Autoimmune thyroid disease (ATD) is caused by the development of autoimmunity against thyroid antigens and comprises Hashimoto's thyroiditis and Graves disease. They are frequently associated with other organ or non-organ specific AIDs, such as myasthenia gravis (MG). In fact, ATD seems to be the most associated pathology to MG. The etiology of both diseases is multifactorial and it is due to genetic and environmental factors, and each of them has specific characteristics. The two pathologies show many commonalities, such as the organ-specificity with a clear pathogenic effect of antibodies, the pathological mechanisms, such as deregulation of the immune system and the implication of the genetic predisposition. They also show some differences, such as the mode of action of the antibodies and therapies. In this review that focuses on ATD and MG, the common features and the differences between the two diseases are discussed.

Keywords: acetylcholine receptor antibodies, interferon type I, germinal centers, genetics, etiology

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****Correspondence:***
Sonia Berrih-Aknin
sonia.berrih-aknin@upmc.fr

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INTRODUCTION

Autoimmune diseases (AIDs) are the result of specific immune responses directed against structures of the self. Under normal conditions, the immune system is tolerant to molecules recognized as "self" and does not react to antigens expressed in endogenous tissues. If self-tolerance is missing, the immune system could develop an immune response against self-molecules, causing the development of AIDs that include autoimmune thyroid diseases (ATDs) and myasthenia gravis (MG).

The etiology of AIDs is multifactorial and involves genetic and environmental factors. ATDs are endocrine diseases due to an autoimmune reaction against thyroid antigens, in a specific genetic background triggered by exposure to environmental factors (1).

The two main ATDs are Graves disease (GD) and Hashimoto's thyroiditis (HT) that are characterized by hypothyroidism and thyrotoxicosis, respectively, by the production of thyroid autoantibodies such as thyroid peroxidase (TPO), thyroglobulin (TG), and thyroid-stimulating hormone receptor (TSHR), as well as by lymphocytic infiltration of the thyroid (1). MG is a neuromuscular disorder due to a defective transmission of the nerve impulse to muscles, causing muscle weakness and abnormal fatigability. In most cases, MG is mediated by antibodies targeting the acetylcholine receptor (AChR) while in a minority of patients, the autoantibodies are specific for muscle-specific kinase (MuSK) or agrin receptor LRP4 (low-density lipoprotein receptor-related protein-4). Other targets, such as titin, and ryanodine, have been investigated (2).

CONCOMITANT THYROIDITIS AND MG: EPIDEMIOLOGICAL FEATURES

The prevalence of ATDs is high and estimated to be 5% in the general population (3) while MG is a rare disease with an incidence of 8–10 cases per one million persons/year and a prevalence of 150–250 cases per one million (4) (**Table 1**). Although ATD is one of the most representative organ-specific autoimmune disorders, it is associated with other autoimmune endocrine failures or non-endocrine diseases (5). Among the non-endocrine diseases, we can mention vitiligo, pernicious anemia, MG, autoimmune gastritis, celiac disease, and hepatitis (6, 7). Interestingly, in these associated diseases, the presence of anti-TPO antibodies is more frequent than the prevalence of ATDs (6).

The aim of this review is to focus on the association between MG and ATDs. The most common diseases coexisting with MG are GD and HT, with a frequency of 7 and 3%, respectively (13). ATDs were diagnosed in 26.8% of MG Polish patients including 4.4% with GD, 9% with HT, and 13.4% with anti-thyroid antibodies (14). In British and German populations, 16% of early-onset MG (EOMG), 9% of late-onset MG, and 17% of thymoma-MG patients had antibodies against TPO or TG (15). About 0.2% of patients affected by ATDs show MG that is much higher than the general incidence of MG (0.01%). MG could be ocular or generalized, even if ATDs are more frequent in the ocular group (16–18). When associated to ATDs, MG shows specific features, such as the young age of onset, mild clinical symptoms, low levels of AChR antibodies, and low frequency of thymic alterations (18–20). These data highlight that the association between MG and ATDs is much more frequent than expected.

ETIOLOGY

The etiology of AIDs is still unknown. Drugs, virus infections, radiation, stress are some of the environmental factors that may be involved in the development of ATDs and MG in susceptible individuals, contributing to the activation of an innate immune response (8, 10, 21, 22).

Factors of Predisposition

Autoimmune thyroid diseases are more common among women than men with a female:male ratio of 5–10:1. There is a difference in prevalence and incidence in the base of geographic area, race, and age. The frequency of anti-thyroid antibodies increases with age, showing a peak ranging from 45 to 55 years. In females, one of the two X chromosomes is inactivated during early embryonic stage (23). The inactivation of the same X chromosome, that occurs in more than 80% of cells, could result in defect in immunological tolerance to X-linked antigens that could lead to autoimmunity. Moreover, fetal microchimerism was observed in blood and thyroid tissues from women with either HT or GD. During pregnancy, the production of maternal regulatory T cells (Treg) early in pregnancy could lead to a decrease in the circulating anti-thyroid antibodies, maintaining a state of tolerance to fetal alloantigens in order to avoid fetus rejection. After birth, anti-thyroid antibodies rebound with a transient increase. The persistence of fetal cells in maternal tissues leads to fetal microchimerism (24).

In MG, instead, the early-onset forms, characterized by the age of onset before 50 years, are more frequent in female than male with a ratio female:male of 3:1. Different studies suggest an important role of estrogens in MG (25), since estrogen receptors are expressed on thymic epithelial cells and on thymocytes (21). The female bias in AIDs could be due to reduced expression by estrogens of AIRE, a transcription factor involved in negative selection, resulting in a decreased quality of autoreactive cells elimination (26).

By case–control studies, and more recent genome-wide association studies, different genes have been associated with the ATDs and MG and the presence of specific autoantibodies. Genes involved in T-cell activation and regulation, such as protein tyrosine phosphatase non-receptor 22 (*PTPN22*), cytotoxic T-lymphocyte antigen-4 (*CTLA4*), and human leukocyte antigens (HLA), are associated with both ATDs and MG. PTPN22 is an intracellular protein tyrosine phosphatase bound to c-src tyrosine kinase, involved in T-cell activation (27); CTLA4 plays a role in inhibiting T-cell signaling, and the HLA is essential for presenting exogenous antigens for recognition by $CD4^+$ T-helper cells (28). Other genes have been associated to a single disease, as indicated in **Figure 1**. Therefore, in both ATDs and MG, factors of predisposition include not only genetic background, but also the potential role of sexual hormones.

Triggering Factors

Hepatitis C virus (HCV) infection is the most associated to ATDs both in adults and children, in fact, infected HCV

TABLE 1 | Epidemiological and clinical features of patients with autoimmune thyroid diseases and myasthenia gravis (MG).

	Hashimoto's thyroiditis	Graves' disease	AChR-MG	MuSK-MG
	Hypothyroidism	Hyperthyroidism		
Incidence	About 2%	About 2%	About 0.1%	About 0.01%
Female/male ratio	Around 10	Around 10	Early onset: F > M (ratio around 3) Late onset: F = M	Around 6
Tissue pathology	Damage of the thyroid gland	Enlarged thyroid (diffuse goiter)	Thymic pathologies, hyperplasia among the young patients, and thymoma among the oldest patients	No thymic pathology
Therapy	Levothyroxine (LT4)	Anti-thyroid drugs, radioactive iodine, and surgery	Anticholinesterase drugs, thymectomy, immunosuppressive drugs (azathioprine, corticosteroids)	Corticosteroids Rituximab

The data on this table were collected from the following Ref. (8–12).

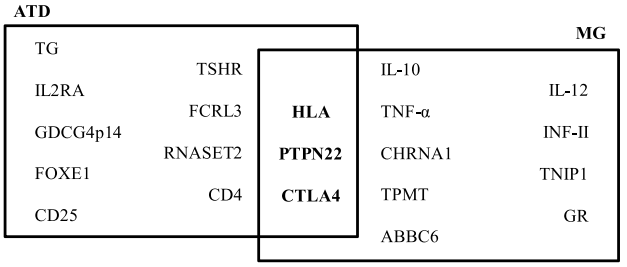

FIGURE 1 | Predisposing genes in autoimmune thyroid diseases (ATDs) and myasthenia gravis (MG). The data on this figure were collected from the following Ref. (28–30).

patients show dysfunctions in the thyroid (10, 31). In patients with chronic hepatitis C (CHC), the thyroid disorders are characterized by an increased risk of ATD and hypothyroidism in females, elevated levels of anti-TPO antibodies, and by papillary thyroid cancer risk (32, 33). The hypothesized mechanism is that HCV envelope protein E2 induces strong inflammatory responses in human thyrocytes, resulting in the production of interleukin (IL)-8, IL-6, and tumor necrosis factor-α (TNF-α). The E2 protein also induces the upregulation of molecules involved in innate immune pathways (34). Also human herpes virus-6 (HHV-6) infection is associated with ATD onset, in fact, a high level of HHV-6 activation marker was found in thyroid tissue of patients with ATD (35). In myasthenic patients, the existence of a chronic inflammatory state in the thymus could alter innate immune responses leading to self-tolerance failure (36–39). The inflammatory state could be due to persistent viral replications, in fact, Epstein Barr virus (EBV), cytomegalovirus, human foamy virus, and Nile virus were found to be associated to MG (40, 41). Pathogen infections could play a role in AIDs through dysregulation of toll-like receptor-mediated innate immune responses, which can result in altered innate immune responses and long-term inflammation, rendering the thymus vulnerable to auto-sensitization (40, 41). EBV is one of the main candidates suspected to play a role in MG initiation, since it is able to promote B-cell abnormal activation and survival, and to disrupt critical B-cell tolerance checkpoints (40, 42–44).

Recent data have confirmed a strong association between ATD development and interferon (IFN)-α therapy in patients with CHC. About 40% of CHC patients acquire thyroid disorders while receiving IFN-α. IFN-induced thyroiditis is visible as clinical thyroiditis in about 15% of HCV patients receiving IFN-α and subclinical thyroiditis in up to 40% of patients (45). Moreover, it was observed that the generation of anti-thyroid antibodies tends to continue also after IFN therapy (30). IFN-α could induce thyroiditis by both direct toxic effects on the thyroid and by immune recruitment mechanisms (46).

Interestingly, IFN-I therapies can also prime the development of MG (47). IFN-I, especially IFN-β, could play a central role in the thymic follicular hyperplasia of MG patients by inducing high expression of α-AChR and of CXCL13 chemokine in thymic epithelial cells, and of the chemokine CCL21 in endothelial lymphatic cells, two chemokines involved in the abnormal recruitment of B cells in EOMG thymuses. IFN-β also increases B-cell activating factor expression, which promotes the development of autoreactive B cells (48). Also, IFN-β overexpression in MG thymus can mediate the effects of dsRNA activation and causes α-AChR subunit overexpression, suggesting that IFN-β can play a central role in MG development (36).

Other drugs can induce AIDs, including immunomodulatory agents used to treat melanoma, such as monoclonal antibodies inhibiting the immune checkpoint pathways, as CTLA4 and programmed cell death protein 1 (PD-1), two-cell surface receptors on T cells which down-regulate immune response (49). Ipilimumab is a human immunostimulatory antibody targeting CTLA4 that can cause thyroiditis and/or hypothyroidism in 6% of cases after several cycles. Pembrolizumab and nivolumab act against PD-1 and, if combined with ipilimumab to inhibit both CLT4 and PD-1, show a stronger effect with thyroiditis in 22% of cases (50).

DIFFERENTIAL AND COMMON FEATURES IN ATDs AND MG

Antibodies

Both MG and ATD diseases are organ specific and antibody-mediated, and both kinds of disorders combine many different pathologies. Patients with ATDs have antibodies against proteins of the thyroid, but the characteristics of the disease differ according to the autoantigen. Patients with HT have serum antibodies reacting with TG, TPO, while patients with GD have antibodies against the receptor of TSH (51) (**Table 2**).

Myasthenia gravis is due to antibodies against the neuromuscular junction (59). Similarly to thyroiditis, in MG, several antigens are the targets of the autoantibodies, and the disease features depend upon the nature of the antibodies. Patients with anti-AChR, but not with anti-MuSK antibodies, have thymic pathologies, hyperplasia among the young patients, and thymoma among the oldest patients (60).

Interestingly, in both MG and ATDs, some forms of the disease are IgG4 dependent, an Ig subclass that does not bind to the complement. In MG, anti-MuSK antibodies are IgG4 (61). In ATDs, several subcategories of IgG4-mediated diseases have been identified including a fibrosing variant of HT, IgG4-related HT, and GD with elevated IgG4 levels (62). These IgG4 diseases share common mechanisms that involve the mechanical interference of extracellular ligand–receptor interactions by the IgG4 antibodies (63).

The mechanisms of action of the antibodies are quite different in MG and ATD, likely due to the nature of the target antigen and its localization. In HT, together with cytotoxic cells, the antibodies contribute to the destruction of the thyroid, leading to hypothyroidism (**Table 2**). In the case of GD, the antibodies against TSHR could be stimulatory, blocking or neutral; when the stimulating antibodies predominate, clinical features become obvious (56). Thus, the antibodies are functional, able to stimulate or to inhibit the secretion of thyroid hormones. Fluctuating antibody levels can lead to syndromes alternating

TABLE 2 | Physiopathological features of patients with autoimmune thyroid diseases and myasthenia gravis (MG).

		Hashimoto's thyroiditis	Graves' disease	AChR-MG	MuSK-MG
Humoral immunity	Target of the autoantibodies	TG (20–50%), TPO (90–95%)	TSHR	AChR	MuSK
	Mechanism of the Abies	Thyroid destruction by cytotoxic cells, death receptors, and impairment of thyroid hormone production	Overactivation of the gland: thyroid stimulatory, blocking, and neutral Abies	AChR blocking, internalization, and degradation	Disruption of neuromuscular junction and inhibition of the retrograde signaling
	Role of complement	Yes	Yes	Yes	No
Cellular mechanisms	Infiltration of the target organ	+++ Thyroid	+ Thyroid, but not destruction	Neg in the muscle +++ in the thymus	Neg in the muscle Neg in the thymus
	Ectopic GC	Yes (thyroid)	Yes (thyroid)	Yes (thymus)	No
	T-cell involvement	Th1, Th17	Th2, Th17	Th1, Th2, Th17	Th1, Th17
	Role of epithelial cells	Overproduction of pro-inflammatory cytokines and chemokines by thyroid epithelial cells		Overproduction of pro-inflammatory cytokines and chemokines by thymic epithelial cells	Unknown
	Regulatory B cells	Normal B10 number	Normal B10 number	Decreased B10 cell number	Decreased B10 cell number

The data on this table were collected from the following Ref. (1, 52–58).

between hyperthyroidism and hypothyroidism (64). In the case of MG, anti-AChR antibodies induce its degradation dependent upon the complement, and its internalization (2), while anti-MuSK antibodies disrupt the neuromuscular junction and inhibit the retrograde signaling (65, 66). Recent findings suggest that the anti-AChR antibodies could also have a functional effect, by inducing the overproduction of IL-6, a cytokine that plays a role in muscle biology (67). It is not clear yet if this mechanism participates to the pathogenic mechanisms or is a compensatory mechanism.

Most of the autoantibodies have a clinical usefulness. Anti-TPO and anti-TSHR antibodies are relevant for the diagnosis of HT and GD, respectively (30, 68). Anti-TSH receptor antibodies are of interest in GD as they correlate with the disease severity and their levels decrease with therapies (69). However, anti-TPO and anti-TG Abs are not unique to HT patients since these antibodies are detectable in the majority of GD patients (70). In the case of MG, the anti-AChR antibodies are very useful for the diagnosis but not for the follow-up. On the other hand, for the group of patients with anti-MuSK antibodies, monitoring its level is relevant, since it correlates with the clinical course (2).

Infiltration of the Target Organ and Germinal Centers

Patients with GD can have an infiltration of the thyroid gland, while in the case of HD, the infiltration is severe and accompanied by the destruction of the thyroid (71). Ectopic B-cell follicles are observed in the thyroid gland in HT (72). Autoreactive B cells within these lymphoid follicles were recognized by their ability to bind thyroid antigens (72). In MG, the neuromuscular junctions displays minimal lymphocytic infiltration, while the thymus at least in the young patients includes many infiltrating cells, signs of inflammation, and germinal centers (53). The degree of hyperplasia is related to the level of anti-AChR antibodies (73).

Immune Dysregulation

In both MG and ATDs, T-cell immune-mediated mechanisms are involved. In ATDs, cellular immunity targeting thyroid antigens is very common (74, 75). This mechanism is also a feature of experimental thyroiditis obtained in animals by injection of thyroid antigen with adjuvants (76). In MG, similar data are observed; in the patients, and in the experimental models of MG, T-cell proliferation using the autoantigen or peptides from the AChR has been shown (77–79).

In addition, inflammatory cells such as Th1 and Th17 were shown to be involved in the different forms of thyroid or myasthenic diseases (**Table 2**). Th1 cytokines are increased in MG patients and its experimental model (EAMG) and normalized with therapies (80, 81). Th1 cells and their cytokines are required for EAMG development (82), through the production of complement-dependent anti-AChR antibodies that are pathogenic (82, 83). In addition, TNF-α has been shown to contribute to the chronic inflammation observed in the MG thymus (84). In ATDs, Th1 cells recruited in the thyroid may be responsible for increased production of IFN-γ and TNF-α, which in turn stimulates the secretion of the pro-inflammatory chemokine CXCL10 from the thyroid cells, resulting in an amplification feedback loop, which could perpetuate the autoimmune process (1). Th17 cells and IL-17 have an inflammatory and pathogenic role in MG and ATD (85). Interestingly, IL-17 also contributes to B-cell responses. Indeed, mice mutated for IL-17 receptor have reduced humoral responses and germinal center development (86). In MG patients, the seric level of IL-17 is increased (84, 87). In the mouse model, IL-17 deficient mice are resistant to develop MG, and the pathogenic anti-murine AChR antibodies are lower compared with wild-type mice (88). In ATDs, an increased differentiation of Th17 lymphocytes and an enhanced synthesis of Th17 cytokines were shown, mainly in HT (89).

Finally, the defects of immune regulation are a hallmark of AIDs. In both MG and thyroiditis, functional defects of Treg

cells have been shown while the cell number is normal (90–92). In addition, there is a shift from Treg cells to Th17 cells, suggesting that Treg/Th17 balance is altered (84, 93). However, in MG, it was also demonstrated that the Teff cells are resistant to suppression (84). To our knowledge, there is no equivalent study in ATDs disorders. The number of B reg cells has been shown to be decreased in MG but not ATDs (55, 58, 94).

Microbiota is essential for immunologic and digestive homeostasis (95) and is involved in many AIDs (52). In animals, the lack of microbiota is associated with reduced intestinal surface areas with shorter villi, changes in mucus layer, and permeability (5, 96), together with reduced B- and T-cell production (97). Interestingly, in humans, a morphological and functional damage of the intestinal barrier was similar in patients bearing type-1 diabetes and with ATD (98). In addition, in hyperthyroid patients, the microbiota composition was shown to be altered (99). This aspect has not yet been investigated in MG.

THERAPIES

Although both MG and ATDs are associated with immune system defects, the treatments are different. In the case of MG, treatments include anticholinesterase molecules and immunosuppressive therapies. Among these therapies are conventional immunosuppressant, such as azathioprine, as well as corticosteroids. Recently, monoclonal antibodies against B lymphocytes have proved interesting (100). In the case of thyroid disease, therapies are aimed at regulating thyroid hormone levels (101). The treatment of choice for HT or hypothyroidism is thyroid hormone replacement. The drug is orally administered usually for life.

Surgery is applied in both pathologies. In MG, thymectomy may be proposed when the thymus is hyperplastic or when a thymoma is associated. Recently, a Thymectomy Trial in Non-Thymomatous MG Patients Receiving Prednisone Therapy was conducted in order understand if transsternal thymectomy with prednisone therapy could be more efficient than prednisone alone after 3 years. An improvement of clinical outcomes over a 3-year period in patients with non-thymomatous MG underwent thymectomy was observed (102). In ATDs, thyroid ablation is recommended in GD when the goiter is large, and in HT when a defined thyroid nodule is present (68). It is interesting to note that in both cases the organ that is operated is inflammatory and contains germinal centers with B lymphocytes participating in the pathogenic response.

CONCLUSION

In conclusion, MG and ATD share many commonalities. They are both organ-specific AIDs with a clear pathogenic effect of antibodies, although ATDs are 50–100 times more frequent than MG disease.

Interestingly, ocular involvement is observed in both pathologies. The pathological mechanisms high up many commonalities, such as deregulation of the immune system and the implication of predisposing genes, such as HLA and *PTNP22* genes. However, the mode of action of the antibodies is different: if the antibodies in ATDs deregulate the level of the hormones, in the case of MG they reduce the expression of receptors at the motor plate leading to a functional defect of the synapse.

It is interesting to note that certain drugs are capable of inducing MG and ATDs, for example, IFN-I or monoclonal antibodies against immune checkpoints have proved to be inducers of these pathologies.

Finally, therapies in MG and ATDs are different. In ATDs, the use of molecules to regulate the level of the hormones is satisfactory. In MG, anticholinesterases are generally insufficient, and immunosuppressive therapy is very frequently associated.

AUTHOR CONTRIBUTIONS

AL and SB-A discussed the content of the review and wrote the manuscript.

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Autoimmune Thyroiditis and Glomerulopathies

Domenico Santoro[1], Carmela Vadalà[1], Rossella Siligato[1], Michele Buemi[1] and Salvatore Benvenga[2]*

[1] Unit of Nephrology and Dialysis, Department of Clinical and Experimental Medicine, University of Messina, Messina, Italy,
[2] Unit of Endocrinology, Department of Clinical and Experimental Medicine, University of Messina, Messina, Italy

Autoimmune thyroiditis (AIT) is generally associated with hypothyroidism. It affects ~2% of the female population and 0.2% of the male population. The evidence of thyroid function- and thyroid autoantibody-unrelated microproteinuria in almost half of patients with AIT and sometimes heavy proteinuria as in the nephrotic syndrome point to a link of AIT with renal disease. The most common renal diseases observed in AIT are membranous nephropathy, membranoproliferative glomerulonephritis, minimal change disease, IgA nephropathy, focal segmental glomerulosclerosis, antineutrophil cytoplasmic autoantibody (ANCA) vasculitis, and amyloidosis. Different hypotheses have been put forward regarding the relationship between AIT and glomerulopathies, and several potential mechanisms for this association have been considered. Glomerular deposition of immunocomplexes of thyroglobulin and autoantibodies as well as the impaired immune tolerance for megalin (a thyrotropin-regulated glycoprotein expressed on thyroid cells) are the most probable mechanisms. Cross-reactivity between antigens in the setting of genetic predisposition has been considered as a potential mechanism that links the described association between ANCA vasculitis and AIT.

Keywords: thyroiditis, Hashimoto, glomerulonephritis, membranous glomerulopathy, vasculitis

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Rauf Latif,
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Laura Gragnani,
University of Florence, Italy
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University of Pisa, Italy

****Correspondence:***
Domenico Santoro
santisi@hotmail.com

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INTRODUCTION

Hashimoto's thyroiditis is the leading form of autoimmune thyroiditis (AIT), which is the most prevalent autoimmune disorder and the most common cause of hypothyroidism, excluding iodine insufficiency. It affects ~2% of the female population and 0.2% of the male population (1). This condition is well known to be associated with other autoimmune diseases, the most common of which are chronic autoimmune gastritis, vitiligo, rheumatoid arthritis, polymyalgia rheumatica, celiac disease, type 1 diabetes, Sjögren's syndrome, systemic lupus erythematosus (SLE), multiple sclerosis, and sarcoidosis (2). Also glomerular disease may be related to autoimmune disease with several mechanisms.

THE EFFECTS OF THYROID HORMONES ON KIDNEY

Thyroid hormone influence on kidney is mediated by its effect on the cardiovascular system and, consequently, by its effect on renal blood flow. Hypothyroidism initially decreases peripheral vascular resistance and blood pressure and subsequently activates the renin–angiotensin–aldosterone system, which increases tubular sodium reabsorption. As a consequence, cardiac preload and vascular resistance raise, resulting in increased diastolic blood pressure and cardiac afterload (3). Renin gene expression is also regulated by circulating levels of free triiodothyronine (FT3) and free

thyroxine (FT4) through beta-adrenergic activation; accordingly, the reduced sensitivity to beta-adrenergic stimulus occurring in hypothyroidism can cooperate with other hemodynamic abnormalities decreasing renin release (4, 5). The resulting negative inotropic effect on the heart, as well as the altered equilibrium between the reduced expression of vasodilators such as vascular endothelial growth factor or insulin-like growth factor-1, can lead to further renal vasoconstriction. Other consequences of thyroid hormone deficiency include lower secretion of atrial natriuretic factor and erythropoietin, therefore reducing further blood volume (6). Glomerular filtration rate (GFR) can thus decrease by up to 40%, with subsequent elevation of serum creatinine, both indices being directly proportional to circulating TSH levels (and therefore directly proportional to the extent of thyroid failure) independent of other confounding factors such as age, sex, body mass index, or comorbidities. Thyroid hormone replacement in patients with overt or subclinical hypothyroidism restores renal function (4, 7–9).

Experimental models of hypothyroid mice show kidney hypotrophy and altered glomerular structure (6). Salomon and colleagues studied the histopathology of renal lesions in a group of seven patients with hypothyroidism of both primary and secondary etiology (10). They discovered a common pattern in the renal biopsies from all seven patients, which was directly proportional to the duration of disease (10). Electron microscopy highlighted the thickening of both glomerular and tubular basement membranes, due in part to widening of the dense layer (*lamina densa*) and in part to considerable enlargement of the inner light layer (*lamina rara interna*); mesangial matrix was increased. Glomerular cells (epithelial, endothelial, and mesangial) presented a variety of osmiophilic inclusions, most of them containing lipid. Tubular cells contain similar inclusions and also homogenous protein reabsorption droplets (10).

Gao et al. (11) measured serum β2-microglobulin, urine β2-microglobulin, albumin, and immunoglobulins in 39 untreated AITD (28 with Graves' disease and 11 with Hashimoto's disease). Microproteinuria was found in 28.6% of patients with Graves' disease and in 45.5% with Hashimoto's disease. Serum β2-microglobulin concentrations were significantly increased in Graves' disease compared with that of controls. They concluded that the renal lesions associated with AIT are present in both the glomerulus (leading to increased glomerular capillary permeability) and the tubulus.

Free triiodothyronine can also influence the expression of structural and regulatory proteins in renal tubuli, particularly Na^+/K^+ ATPase and Ca^{2+} and Na^+/H^+ exchanger, which have a reduced activity in animal models of long-term hypothyroidism (12). These animals also have increased urinary excretion of sodium and bicarbonate, and defective urinary acidification. Lower medullary hypertonicity results in impaired urinary concentrating ability. On the other hand, increased sensitivity to vasopressin can stimulate water reabsorption (13). Moreover, the filtrate overload caused by altered tubular reabsorption processes, as well as the dysregulation of chloride channels ClC-2, are responsible for the activation of tubuloglomerular feedback, which has important effects on GFR (14). Another important feature of hypothyroid murine models was the increased vascular calcification related to the lower expression of the matrix Gla protein, which physiologically exerts a protective role on vascular calcification (15).

MECHANISMS OF AUTOIMMUNITY IN KIDNEY DISEASE

Kidney can be the victim of autoimmune processes through several mechanisms. Autoantibodies can damage glomeruli either targeting specific antigens as in membranous glomerulonephritis (16) and in anti-glomerular basement membrane (GBM) nephropathy (17), or being trapped through the filtration barrier as in anti-neutrophil cytoplasmic autoantibody (ANCA) vasculitis (18) or IgA nephropathy (19). Pathophysiology of renal impairment in the course of SLE is characterized by both events, because anti-DNA antibodies are located in capillary membranes and mesangial areas of glomeruli and because they cross-react with α-actinin and glycosaminoglycans on mesangial cells (20). All these immune complexes alter the structure of basement membrane, podocyte function, and activate the classical pathway of complement system, which exacerbate the inflammatory process due to chemotactic factors C3a and C5a. In addition, terminal pathway of complement worsens cell damage because of the cytolytic effect of C5b-9 complex (21). Finally, immune complexes stimulate infiltration of innate and specific immune cells, such as neutrophils, macrophages, natural killer (NK) cells, and T lymphocytes, which express receptors for constant fraction (FcR) (22, 23).

Natural killer cells have also a role in the pathogenesis of kidney damage as they produce interferon γ (IFNγ) and activate peripheral macrophages first and, then, resident glomerular cells that are responsible of chronic processes (24, 25).

Kidney-resident dendritic cells secrete IL-23 to recruit both γδ T cells, a specific T subset with adaptive and innate features and a pro-inflammatory role consisting in regulatory T cells (T_{reg}) inhibition, stimulation of B lymphocyte antibodies production and the secretion of cytokines (26). In particular, γδ T cells and double-negative $CD4^-CD8^-$ T cells sustain production of IL-17, which is responsible for neutrophils recruitment. They, in turn, have a central role in damaging kidney through the programmed cell death of neutrophil extracellular traps (NETosis) and the production of reactive oxygen species that stimulate mesangial cell proliferation and cytotoxicity mechanisms (27–29). In addition, IL-17 promotes expression of C-C motif chemokine 20 (CCL20) on mesangial cells, that recruit T helper cells producing IL-17 (T_H17). T_H17 are able to maintain kidney damage and promote B-cell activation through the secretion of IL-21 (30). Finally, T follicular helper cells, a subpopulation of $CD4^+$ that is increased in autoimmune processes, act as stimulator of B cell differentiation into plasma cells (31–33).

T_H1 lymphocytes and IFNγ stimulate macrophage recruitment in SLE- and ANCA-associated vasculitis, as well as anti-GBM nephropathy in experimental models. However, the role of T_H1 lymphocytes in human autoimmune renal disease is not clearly defined yet (34–36). $CD8^+$ T cells have a pathogenic role in ANCA-associated vasculitis, since they can produce both IFNγ and tumor necrosis factor (37). The presence of $CD8^+$ T cells is also correlated with poor prognosis (38).

Regulatory T cells as well as NKT cells act as regulators of immune response and are reduced in autoimmune disease (39, 40).

GLOMERULAR DISEASE RELATED TO AIT

Glomerular involvement in patients with AIT can occur in 10–30% of cases (41). A retrospective study on 28 patients with Hashimoto's thyroiditis and hematuria, proteinuria, or renal impairment showed that the most common associated kidney diseases are membranous glomerulonephritis (20%), focal segmental glomerulosclerosis (20%), IgA nephropathy (15%), chronic glomerulonephritis (15%), minimal change disease (10%), and amyloidosis (5%). In 15% of the 28 patients, no specific diagnosis was made (42). Other case reports revealed the less frequent connection between AIT and membranoproliferative glomerulonephritis and ANCA vasculitis (43–47) (**Figure 1**).

Various hypotheses were considered to explain the underlying mechanism that links AIT to glomerular lesions and their variable presentation (**Table 1**).

The higher prevalence of membranous nephropathy (MN) suggests a plausible immunologic role of thyroid antigens, particularly thyroglobulin (TG) and thyroperoxidase (TPO). Both of them are released in the course of AIT and are found in subepithelial immune deposits, as part of the characteristic spikes of MN (47, 48). At present, there are two possible mechanisms that can explain the immunologic role of thyroid antigens in the pathogenesis of MN: (1) *in situ* immune response against TG deposition at subepithelial level and (2) circulating immune complexes (TG–anti-TG) that can be trapped at subendothelial level due to increased glomerular permeability. As stated before, the pathogenicity of immune complexes in MN is related to their subepithelial localization, but how they could cross GBM remains unexplained. Most likely, immune complexes could dissociate in the subendothelial space and then they would reassemble on the subepithelial side. IgG4 is considered the main antibody subclass deposited in the course of idiopathic MN. Specific subclass of anti-TG and anti-TPO antibodies should be determined in patients with suspicious AIT-related glomerulopathy to distinguish between a clear diagnosis of idiopathic MN or a possible IgG4-mediated secondary form of MN. Moreover, IgG4 antibodies have low affinity for the antigen, which could explain the possible dissociation and reassociation of the IgG4 complexes through the GBM (49).

Other theories involve the mechanism of epitope spreading, a phenomenon that follows the primary immune response against specific epitopes. When the immunodominant response fails to clear the target, the immune system mounts a broader inflammatory response against different epitopes either on the same or on different molecules. Therefore, immune-mediated glomerular disease would be caused by a subset of autoantibodies directed toward epitopes of TG or TPO as well as epitopes of glomerular antigens. This phenomenon may be relevant to the pathogenesis of kidney disease, since in Heymann nephritis (a murine experimental model of membranous glomerulonephritis) the onset of proteinuria correlates with intramolecular epitope spreading (50). In addition, epitope spreading has already been demonstrated in experimental immunization with an immunogenic TG peptide, but has not been investigated in patients yet (51).

The experimental Heymann model also suggests megalin (gp330) as a possible immunologic target involved in the immunopathogenesis of glomerular injury during AIT. Megalin is a large glycoprotein receptor expressed on thyrocytes in a TSH-dependent manner, but it is also expressed on the renal proximal tubular cells (52). Megalin is a receptor that interacts with various intracellular adaptor proteins for intracellular trafficking and that functions cooperatively with other membrane molecules (52). Megalin is involved in the uptake of glomerular-filtered albumin and other molecules such as insulin, hemoglobin, vitamin D-binding protein, retinol-binding protein, and β_2-microglobulin. In addition, a number of toxic substances, such as glycated proteins (AGEs), myeloma light chain, and aminoglycosides, undergo megalin-mediated endocytosis, leading to cell damage (52). AIT could determine a rupture of immune tolerance toward this self-antigen, thus causing an immune response on podocytes.

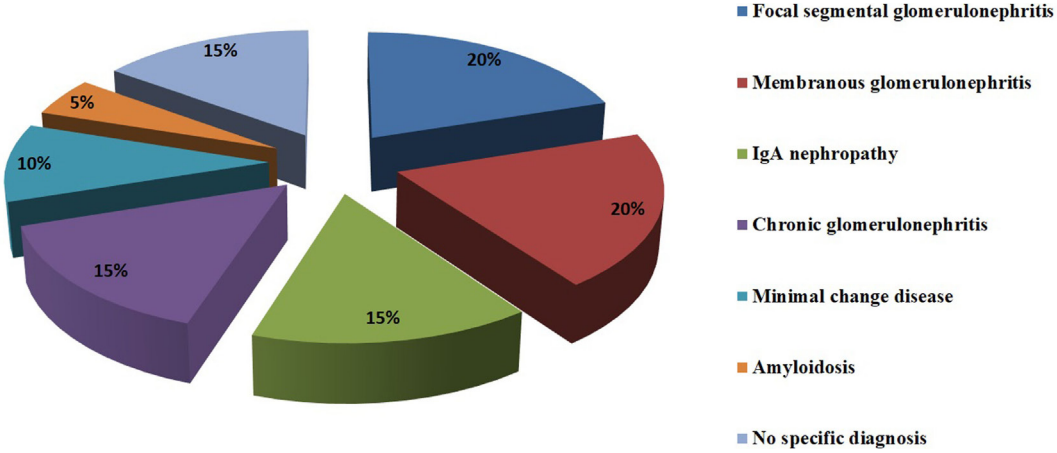

FIGURE 1 | Glomerulopathies associated with HT.

TABLE 1 | Mechanisms underlying the relationship between HT and kidney disease.

In situ immune response against thyroglobulin (TG) deposition at subepithelial level
Circulating TG–anti-TG complexes trapped at subendothelial level due to increased glomerular permeability
Megalin (gp330) as a possible immunologic target
Epitope spreading
Genetic predisposition and cross-reactivity between antigens

The relationship between AIT and ANCA vasculitis was shown by Lionaki and colleagues (53). In their case–control study, they demonstrated that when ANCA vasculitis was diagnosed, as many as 40% of women had thyroid disease. Among men, the prevalence of thyroid disease was lower. Patients with positive anamnesis for thyroid disease were more likely to have myeloperoxidase (MPO)-ANCA (86%) than proteinase 3-ANCA (14%) (53). Both genetic predisposition and cross-reactivity between antigens have been hypothesized as potential mechanisms for this association. A functional polymorphism in the protein tyrosine phosphatase gene, the *PTPN22* 620W allele has been recognized as a predisposing factor for several autoimmune disorders, including AITD, Wegener's granulomatosis, and ANCA positivity (54–56). *PTPN22* is located on chromosome 1p13.3–13.1.10 and encodes an 807-amino acid protein that interacts with Csk, a tyrosine kinase that is involved in the intracellular signaling cascade following T-cell activation. A missense variation in the autoimmunity-predisposing allele results in gain of function that increases the threshold for T-cell receptor signaling (57). As in other multifactorial processes, one or more environmental triggers are necessary for the full development of the disease. Occupational exposures to factors such as silica (58) showed an association with ANCA vasculitis, while infections such as *Yersinia enterocolitica* or retroviruses have been postulated to participate in the pathogenesis of AITD (56). Eventually, cross-reactivity between TPO and MPO may be another mechanism involved in the development of autoimmunity, due to the strong homology between amino acids 586–601 of TPO and amino acids 594–609 of MPO (59, 60).

Type 1 diabetes mellitus (DM1), a known autoimmune disease that can be present in 3–8% of patients with Hashimoto's thyroiditis (61) and in 6–10% of subjects with Graves' disease (62), is worth mentioning at this point. Benvenga et al. investigated the presence of serum antibodies directed against one or both thyroid hormones (THAbs), which are considered to be rare autoantibodies, in a cohort of 52 DM1 patients both at baseline and after 6 years of follow-up (63). They found that serum THAb could be predictive for concurrent or subsequent DM1-related complications, including diabetic nephropathy. Patients already affected by nephropathy showed either T3IgG or T4IgM at baseline. T4IgM was associated with a high rate of retinopathy (67%), nephropathy (50%), and neuropathy (33%). At tissue level (kidney, in this particular case), THAb may decrease the local availability of thyroid hormones, not much differently from the decreased tissue availability resulting from the decreased thyroid output of thyroid hormones. Clearly, this study (63) awaits confirmation by future investigations.

Finally, renal diseases presenting as nephrotic syndrome can lead to the onset or the aggravation of preexisting hypothyroidism. The urinary loss of both protein-unbound (free) and protein-bound thyroid hormones, with consequent decreased serum levels of T4, T3, FT4, FT3, and major carrier proteins (thyroxine-binding protein, transthyretin, and albumin), is directly proportional to proteinuria. The practical consequence of this urinary loss is the increased requirements of the daily L-T4 replacement (64).

CONCLUSION

A relationship between AIT and glomerulonephritis does exist, but it requires further investigations in larger cohorts. A common pathogenesis may be considered, especially in patients with simultaneous appearance of glomerular and thyroid dysfunction. Monitoring kidney function should be considered as part of the follow-up of AIT patients, particularly of those with HT-related hypothyroidism.

AUTHOR CONTRIBUTIONS

Conceptualization: DS, CV, RS, and SB. Research literature: DS and MB. Methodology: DS and RS. Supervision: DS, MB, and SB. Writing original draft: DS, CV, and RS.

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The Association of Sjögren Syndrome and Autoimmune Thyroid Disorders

Chiara Baldini[1], Francesco Ferro[1], Marta Mosca[1], Poupak Fallahi[2] and Alessandro Antonelli[2]*

[1] Rheumatology Unit, University of Pisa, Pisa, Italy, [2] Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy

Sjögren's syndrome (SS) and autoimmune thyroid diseases (AITD) may frequently coexist in clinical practice, resulting in a complex overlapping disorder that represents a particular example of the expression of heterogeneity in patients with autoimmune disorders. Objective of this review was to describe the prevalence of the SS–AITD association in the most recent literature, exploring in particular to what extent the presence of AITD might influence the clinical expression of SS and *vice versa*. Moreover, we summarized some of the proposed genetic, biologic, and molecular mechanisms implied in the pathogenesis of AITD–SS association. Finally, we explored risk factors for lymphoma development in both AITD and SS. We performed a Medline search of English language articles published in the PubMed database in order to provide a critical overview of the recent literature on pathogenesis and clinical features of AITD–SS overlapping disease. All the articles were critically analyzed to select the most relevant contributions.

Keywords: Sjögren's syndrome, autoimmune thyroid diseases, non-Hodgkin's lymphoma, comorbidities, pathogenesis

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****Correspondence:***
Chiara Baldini
chiara.baldini74@gmail.com

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INTRODUCTION

Sjögren's syndrome (SS) is a complex and heterogeneous autoimmune disease that frequently co-occurs with both organ-specific and non-organ specific, systemic rheumatic diseases (i.e., rheumatoid arthritis, systemic lupus erythematosus, and systemic sclerosis) offering a unique opportunity to investigate pathogenesis, long-term-evolution, and outcome of different autoimmune phenotypes and subsets (1–5).

The association of SS and autoimmune thyroid diseases (AITD) has been largely documented, suggesting that AITD could be overrepresented in patient with SS with respect to general population and *vice versa* (6). Interestingly, Rojas-Villarraga et al. (7) analyzing prevalence of multiple autoimmune syndromes in 1,083 patients belonging to four autoimmune disease cohorts described AITD and SS as the most frequent coexisting autoimmune disorders in single patients. Overall, then, it has been hypothesized that common genetic, immunologic, and biologic factors may be implied in SS and AITD, leading to the coexistence of these two conditions (8). Moreover, both SS and AITD may lead to the development of non-Hodgkin's lymphoma (NHL) highlighting the relationship between similar autoimmunity pathways and lymphoproliferation (9, 10). Although the majority of data support an increased prevalence of AITD in SS patients, some authors have suggested that this observation might be related to the age and sex distribution of SS and AITD rather than representing a true association. However, literature data are difficult to compare due to the fact that different SS classification criteria and AITD definitions have been utilized over the years, making it difficult to define the exact prevalence of SS–AITD association (11, 12).

In this review, we aimed at describing the frequency of the SS–AITD association in the most recent literature, exploring, in particular, to what extent the presence of AITD may influence the clinical expression of SS. Moreover, we will summarize some of the proposed pathogenetic mechanisms for the coincidence of SS and AITD and the common biologic factors involved into lymphoproliferative complications.

Prevalence of SS in AITD: A Clinical Spectrum Ranging From Isolated Sicca Symptoms to Full-Blown SS

Autoimmune thyroid diseases, namely, Hashimoto's thyroiditis (HT) and Graves' disease (GD), are organ-specific autoimmune disorders, essentially resulting from a T cell-mediated immune attack of the thyroid resulting into lymphocytic infiltration of the thyroid parenchyma (13). The association between AITD and other organ specific (polyglandular autoimmune syndromes), or systemic rheumatic disorders has been widely described. SS is perhaps the most frequently rheumatic autoimmune disease associated with AITD, and particularly with HT. Several authors have reported that a full-blown SS could be 10 times higher in AITD than in the general population (14). In fact, the prevalence of SS in AITD has been assessed by several heterogeneous studies over the time and apparently varies from 3% up to 32% (15–17).

In 1992, Warfvinge et al. (18), analyzing different degrees of morphologic and functional salivary gland changes in AITD, found that 11 patients out of 19 presented xerostomia, a compromised unstimulated salivary flow and alterations of their lower lip biopsy, and/or parotid scintigraphy. Six of them presented a true SS. Similarly, Tektonidou (16) in a cohort of 58 patients with antinuclear antibodies positive AITD found that 9% fulfilled the criteria for SS. These data on small cohorts were confirmed also in large population studies over the years. For example, Biro et al. (19) evaluating the prevalence of SS in 426 patients with HT or GD found that SS had a prevalence of 17% in HT and of 5% in GD. Similarly, Lu et al. (20) observed that the risk of SS in patients with thyroiditis was 3.6 times higher than in individuals without thyroiditis.

The spectrum of sicca symptoms in patients with AITD that do not fulfill the criteria for SS is even more common. More specifically, Coll et al. (21) in a cohort of 176 patients with AITD found that 19 of 52 (37%) patients presented isolated xerostomia and 39/170 (23%) isolated keratoconjunctivitis sicca. Other authors described an isolated positivity for antinuclear antibodies in 25–55% of patients with AITD. The real implication of antinuclear antibodies positivity in AITD patients has to be clarified, but it is generally believed that they may reflect polyclonal activation and antibody production that over time may trigger the development of concomitant systemic autoimmune diseases including SS (22). In clinical settings, patients with AITD and a positivity for antinuclear antibodies should then be monitored more closely for the development of SS during the follow-up.

Overall, the available literature suggests that both a full blown SS and "incomplete" subsets of SS may be quite common among patients with AITD. Among these incomplete forms, an important differential diagnosis is represented by patients with sicca symptoms, affected by fibromyalgia. Patients with fibromyalgia often present dry eyes and dry mouth and noteworthy, they may present AITD or a positivity for thyroid auto antibodies as well. In the study by Mavragani et al. (23), fibromyalgia patients with sicca symptoms presented thyroid auto antibodies with a prevalence of 60%. Besides fibromyalgia, a number of other systemic disorders associated with AITD also involves salivary glands and should be considered as well in the differential diagnosis. Infectious diseases like hepatitis C virus and Ebstein B virus infections are among the major mimickers of SS in AITD patients, especially due to viral lymphotropism and epithelial tropism (24, 25). Immune disorders including sarcoidosis and IgG4 disease may be considered as well. The latter represents a novel entity characterized by high serum IgG4 and IgG4 plasma cell-mediated fibro-inflammatory lesions that may involve not only thyroid but also lung, pancreas, kidney, and salivary and lacrymal glands (26). More specifically, IgG4 has been linked to four types of thyroid diseases including: Riedel's thyroiditis, fibrosing variant of Hashimoto's thyroiditis, IgG4-related Hashimoto's thyroiditis, and GD with elevated IgG4 levels (27). The pathogenetic role of IgG4 in these IgG4-related thyroid diseases, however, still remains poorly understood. Those patients may often present with an SS-like subacute diffuse enlargement of lacrymal and salivary glands and sicca symptoms. A minor salivary gland biopsy is often necessary to distinguish IgG4 disease from SS (28, 29).

Prevalence of AITD in SS: A Specific Subset of the Disease?

Several uncontrolled studies have described the presence of AITD in SS with frequencies ranging between 10 and 30% (8). **Table 1** summarizes the most important studies reporting frequency of AITD in SS. The differences observed among these studies might be linked to the different ethnic origin of the patients or to the diagnostic criteria adopted for both SS and HT classification.

TABLE 1 | Prevalence of AITD in Sjögren's syndrome.

Reference	Year	No. PTs	Prevalence (%)			
			HT	GD	Anti-TPO	Anti-Tg
Karsh et al. (30)	1980	24	nd	nd	41.6	20.8
Kelly et al. (31)	1991	100	14	nd	40	nd
Hansen et al. (32)	1991	28	18	nd	36	nd
Bouanani et al. (33)	1991	26	11.5	nd	nd	100
Foster et al. (34)	1993	42	nd	nd	36	36
Perez et al. (35)	1995	33	24	6	45	18
Punzi et al. (36)	1996	121	7	nd	17.6	13.4
Davidson et al. (37)	1999	74	nd	nd	22.8	nd
Ramos Casals et al. (38)	2000	160	20	1.25	15.6	12.5
D'Arbonneau et al. (39)	2003	137	14.6	0.7	10.9	2.9
Tunc et al. (40)	2004	53	4	nd	9	9
Lazarus and Isenberg (41)	2005	114	16	1.8	nd	nd
Biro et al. (19)	2006	400	7	3	nd	nd
Mavragani et al. (11)	2009	54	nd	nd	20.4	18.5
Zeher et al. (42)	2009	479	6.3	3.8	nd	nd
Caramaschi et al. (43)	2013	100	27	nd	nd	nd

nd, not done; HT, Hashimoto's thyroiditis; GD, Graves' disease; Anti-TPO, anti thyroperoxidase antibodies; anti-Tg, antithyroglobulin antibodies, PTs, patients.

As far as the clinical manifestation of AITD in SS, three studies are particularly relevant. In the study by Lazarus and Isenberg (41), 16% of the SS patients developed AITD. The most common clinical manifestation of AITD in SS was hypothyroidism, even though subclinical AITD was probably more common. In the vast majority of the cases, hypothyroidism had been diagnosed before the diagnosis of SS: similarly, Jara et al. (6) in a cohort of 160 primary SS patients found evidence of thyroid disease in 36% of patients: 20% were diagnosed as AITD and 16% were diagnosed as non-AITD. The clinical pattern in more than half of primary SS patients was subclinical hypothyroidism. Finally, in the study by Zeher et al. (42) 479 patients with pSS were investigated with regard to several types of thyroid disease. Overall, thyroid dysfunction was found in 95 patients (21.25%). Apparently, the diagnosis of HT and GD may be present either before or after the onset of SS but, differently from the study by Lazarus and Isenberg (41), both HT and GD were more likely to follow SS. The authors found that in 50% of the cases SS preceded HT by 5.5 years. Interestingly, D'Arbonneau et al. (39) showed that the presence of thyroid-related autoantibodies represented a risk factor for development of AITD during follow-up.

Finally, regarding the clinical impact of AITD on the clinical course, literature data are quite heterogeneous especially due to different control groups that have been included (i.e., SS–AITD versus SS without AITD; SS–AITD versus AITD) and to the classification criteria adopted to define SS. However, Caramaschi et al. (43) demonstrated that the association of AITD in patients suffering from SS defined a subset of patients with milder disease and normal complement 4 levels. More specifically, patients with AITD–SS had less evidence of cryoglobulins, palpable purpura, peripheral neuropathy, and lymphoma. This observation has been confirmed by several additional studies. However, it is nowadays widely accepted that AITD–SS patients are at a greater risk of developing additional autoimmune diseases such as autoimmune liver diseases, inflammatory bowel diseases, and systemic lupus erythematosus and should be closely monitored over the follow-up due to their tendency to present widespread disorders of their immune systems.

SS and AITD: Common Pathogenetic Mechanisms From Epithelitis to Non-Hodgkin Lymphoma

A large amount of data have highlighted that AITD and SS can be considered as pathogenetically correlated. First of all, these two disorders are characterized by similar histological features with a tissue infiltrate that consists primarily of CD4+ T lymphocytes and the possible formation of germinal center-like structures unrevealing B cell activation (8). Second, from a genetic point of view, the two conditions present a similar background with thyroid and epithelial cells expressing the same HLA molecules class II: HLA-B8 and HLA-DR3 (8). In particular, HLA-B8 and -DR3 haplotypes have been reported with a higher frequency in both primary SS and AITD whereas cytotoxic T lymphocytic antigen 4 gene polymorphisms have been reported more frequently in patients with AITD and other autoimmune diseases including rheumatoid arthritis (15).

A third point to take into account is the existence of animal models that spontaneously develop both SS and AITD. Thyroiditis and SS in NOD.H-2h4 mice are chronic autoimmune diseases that develop relatively early in life and persist for the life of the animal making them an excellent model to test therapeutic protocols over a long period of time (44).

Another point reinforcing the pathogenetical link between AITD and SS is represented by the crucial role of the epithelial cells in orchestrating the tissue inflammation and the involvement of several regulatory chemokines, such as the IFN-γ-inducible protein 10 (IP-10/CXCL10) in initiating and perpetuating the autoimmune process. CXCL10 exerts its function through binding to chemokine (C-X-C motif) receptor 3 (CXCR3), and its production is stimulated by IFN-γ and TNF-α, whose production in turn is provided by T helper 1 cells (Th1) (45).

In AITD, it has been postulated that CXCL10 could be a marker of a stronger and more aggressive inflammatory response, subsequently leading to thyroid destruction and hypothyroidism (45). Similarly, epithelial cells from SS patients apparently produce CXCL9 and CXCL10 as well, while most of the CD3+ lymphocytes in periductal foci express CXCR3, thus contributing to salivary gland damage (46).

Another cytokine that exerts a fundamental role in the pathogenesis of both AITD and SS is B-cell activating factor that seems to be especially important for the survival of autoreactive B cells (47). Serum B-cell activating factor concentrations were described as significantly higher in GD and correlated with serum antithyroglobulin antibodies (48). B-cell activating factor has been also correlated to disease activity and severity in SS exerting a key role in lymphoproliferative complications (49–52).

Not surprisingly, both AITD and SS may evolve into B-cell NHLs of salivary glands and thyroid, with a prevalence of 0.5 and 5%, respectively (9). Intriguingly cases of patients with AITD, SS, and NHL have been described even if the vast majority of the studies seem to support the evidence that AITD–SS patients have a lower risk of developing NHL compared to SS patients without AITD (53–56). It remains a matter of debate whether the presence of SS in AITD patients may increase the risk of thyroid lymphoma in AITD patients.

The striking association between SS, AITD, and NHL has provided valuable insights into the relationship between autoimmunity and lymphoproliferation. In this multistep process, key players are represented by chronic inflammation and sustained antigenic stimulation that are apparently able to promote B-cell activation and proliferation. Immune deregulation, moreover, sometimes promotes B cell proliferation mediated by infectious agents (i.e., suppression/dysregulation of T-cells leading to EBV-driven B-cell proliferation) (57, 58). Ultimately, SS and AITD seem to be characterized by a wide spectrum of genetic and molecular abnormalities that culminate in uncontrolled B-cell activation, proliferation, and neoplastic transformation.

Conclusion

The coexistence of SS and AITD occurs frequently in clinical practice probably due to common pathogenetic mechanisms shared by these two conditions. From a practical point of view, it is important to screen patients with SS for AITD and *vice versa*

because the presence of the two disorders may influence patients' clinical presentation and long-term outcome. It is widely accepted that AITD–SS patients may have a milder phenotype of SS with a lower risk for lymphoma development. However, it remains unclear whether a concomitant diagnosis of SS may increase or not the risk for thyroid lymphoproliferative complications in AITD patients. Intriguingly, AITD–SS patients over the follow up frequently present additional autoimmune diseases and should be closely monitored especially for liver autoimmunity. Further studies are warranted to explore genetic, biologic, and molecular factors underlying the SS–AITD association in order to provide further insights for the comprehension of this complex and varied subset of autoimmunity.

AUTHOR CONTRIBUTIONS

CB, FF, MM, PF, and AA gave substantial contribution in the conception and design of the work, in the literature research and in writing the paper; gave the final approval of the version to be published; agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. CB, AA, and PF revised it critically.

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Associations between Systemic Sclerosis and Thyroid Diseases

Poupak Fallahi[1], Ilaria Ruffilli[1], Dilia Giuggioli[2], Michele Colaci[2], Silvia Martina Ferrari[1], Alessandro Antonelli[1] and Clodoveo Ferri[2]*

[1] Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy, [2] Department of Medical, Surgical, Maternal, Pediatric and Adult Sciences, University of Modena and Reggio Emilia, Modena, Italy

We have reviewed scientific literature about the association of systemic sclerosis (SSc) and thyroid disorders. A high incidence, and prevalence, of new cases of autoimmune thyroiditis (AT) and/or hypothyroidism have been shown in sclerodermic patients (overall in the female gender). An association among a Th1 immune-predominance, low vitamin D levels, and AT have been also shown in SSc patients. Cases of Graves' disease (GD) have been described in SSc patients, too, according with the higher prevalence of thyroid autoimmunity. It has been also shown a higher prevalence of papillary thyroid cancer (PTC), in association with AT, in SSc patients. However, in order to confirm results about GD and thyroid cancer, studies in larger number of patients with SSc are needed. During the follow-up of SSc patients it would be appropriate to monitor carefully their thyroid status. The abovementioned data strongly suggest a periodic thyroid function follow-up in female SSc patients [showing a borderline high (although in the normal range) thyroid-stimulating hormone level, antithyroid peroxidase antibody positivity, and a small thyroid with a hypoechoic pattern], and, when necessary, appropriate treatments. In conclusion, most of the studies show an association among SSc, AT, and hypothyroidism, such as an increased prevalence of TC overall in SSc patients with AT. Only few cases of GD have been also described in SSc.

Keywords: systemic sclerosis, autoimmune thyroiditis, hypothyroidism, Graves' disease, thyroid cancer, antithyroperoxidase antibodies, antithyroglobulin antibodies, CXCL10

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****Correspondence:***
Poupak Fallahi
poupak@int.med.unipi.it

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INTRODUCTION

Systemic sclerosis (SSc) is a connective tissue disease characterized by degenerative microvascular phenomena and immune system activation, that lead to fibrosis of the skin and internal organs (1, 2). SSc is clinically a multifaceted disorder derived from different contributions of the abovementioned pathogenetic mechanisms, through a multistep process that causes various clinical phenotypes (3). SSc is a heterogeneous autoimmune disease which has defined by three hallmarks: small vessel vasculopathy, production of autoantibodies, and fibroblast dysfunction. The exact etiology of the disease remains unknown, due to the complex nature of the cellular signaling pathways involved. However, there is strong and consistent evidence that the innate system, in particular

Abbreviations: AbTg, antithyroglobulin antibodies; AbTPO, antithyroid peroxidase antibodies; AITD, autoimmune thyroid disorders; AT, autoimmune thyroiditis; ATA, antithyroid antibodies; dcSSC, diffuse cutaneous scleroderma; FT3, free triiodothyronine; FT4, free thyroxine; GD, Graves' disease; HC, healthy controls; HT, Hashimoto's thyroiditis; lSSc, limited cutaneous scleroderma; MCTD, mixed connective tissue disease; OA, osteoarthritis; OR, odds ratios; PM/DM, polymyositis/dermatomyositis; PTC, papillary thyroid cancer; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; SS, Sjögren's syndrome; SSc, systemic sclerosis; TC, thyroid cancer; TSH, thyroid-stimulating hormone.

toll-like receptor signaling, is contributing to the progression and perhaps onset of SSc (4).

Two overlapping SSc forms exist: (a) a limited cutaneous scleroderma (lSSc), confined to the skin of face, hands and feet and (b) a diffuse cutaneous scleroderma (dcSSc), extended over other areas of the skin, that can involve visceral organs, as kidneys, lungs, heart, and gastrointestinal tract. Patients affected by the limited form show a good prognosis, with a 10-year survival in about 75% of patients; however, about 10% of them develop pulmonary arterial hypertension after 15 years. Patients with dcSSc have a 10-year survival of 55%; death is commonly associated with pulmonary, heart, and kidney involvement.

The diagnosis is established on the basis of clinical suspicion, the presence of autoantibodies (in particular anticentromere and anti-scl70/antitopoisomerase antibodies) and quite rarely on biopsy. Regarding the antibodies, 90% of SSc patients have a detectable antinuclear antibody; anticentromere antibody is more frequent in lSSc (80–90%) compared to dcSSc (10%), and anti-scl70 is more common in dcSSc (30–40%) (5).

The American College of Rheumatology set the diagnostic criteria for scleroderma in 1980 (6).

Systemic sclerosis is associated with significant morbidity (including skin thickening, finger ulcers, joint contractures, pulmonary fibrosis and hypertension, chronic diarrhea, and renal failure) (7).

Systemic sclerosis patients have high rates of symptoms of depression, and SSc is associated with substantially reduced health-related quality of life (8).

Many studies show a high prevalence of autoimmune thyroid disorders (AITDs) in SSc patients; however, contradictory results have been reported too. Here, we review the scientific literature about the possible association of SSc with autoimmune thyroiditis (AT), Graves' disease (GD), and also thyroid cancer (TC).

SSc AND AT

After the initial case reports (9, 10), the association of SSc and AITD has been evaluated by many studies (**Table 1**).

A first systematic study (11) reviewed patients with fatal SSc about pathologic and serologic evidence of thyroid disorders. Histologic evidence of severe fibrosis of the thyroid was reported in 14% of 56 SSc cases (versus 2% of age- and gender-matched control autopsy series). Among 27 SSc patients in whom thyroid-stimulating hormone (TSH) and free thyroid hormones were measured, 7 (26%) were hypothyroid, and 9 had euthyroid sick syndrome. Hypothyroid patients had thyroid glands with fibrosis, but a few lymphocytic infiltration. However, 6/7 of hypothyroid patients had elevated levels of circulating antithyroglobulin antibodies (AbTg). These findings suggested a thyroid autoimmune process leading to gland fibrosis and hypothyroidism in severe SSc patients.

A second study (12) found decreased free thyroxine (FT4), decreased free triiodothyronine (FT3), and increased TSH in 42 SSc patients, versus age and gender controls. However, changes in FT4, FT3, and TSH were small with mean values within normal ranges, suggesting a subclinical thyroid dysfunction.

In a further study, 77 SSc patients were evaluated by measurements of basal FT4, FT3, TSH, and the TSH response to thyrotropin-releasing hormone (13). Eight patients (10%) were hypothyroid. Antithyroid antibodies (ATA) were present in four of eight (50%) of the hypothyroid patients.

Among 39 SSc patients (14), 2 patients had clinical hypothyroidism, while 7 had subclinical hypothyroidism. On the whole

TABLE 1 | Prevalence of thyroid autoimmunity in SSc patients versus controls, in the published studies that included an internal control group.

Reference	SSc patients (*n*)	AITD% in SSc patients	Controls (*n*)	AITD% in controls	*P*
Gordon et al. (11)	56	14	56	2	<0.05
Shahin et al. (17)	24	Serum levels of FT4 in patients were significantly lower than in controls (7.46 ± 2.7 for patients versus 10.5 ± 1.8 for controls with $P < 0.001$). Of the 24 patients, 8 (33.3%) showed hypothyroidism, evidenced by decreased FT4 and increased TSH beyond normal ranges, 5/14 (32.7%) with dSSc versus 3/10 (30%) with lSSc (P = ns)	15		
Innocencio et al. (18)	25	52	113	3.5	
Antonelli et al. (20)	F 184; M 18	F 107/77 (58%); M 7/11 (39%)	F 368; M 36	F 100/268 (27%); M 2/34 (6%)	F 0.0001; M 0.0019
Marasini et al. (21)	79	AbTg in 14% of patients; AbTPO in 23% of patients	81 women with OA serving as controls	AbTg in 13% of patients; AbTPO in 11% of patients	ns (for AbTg); 0.057 (for AbTPO)
Danielides et al. (23)	138	AbTPO and/or AbTg positive in 29% of patients	100	AbTPO and/or AbTg positive in 29% of controls	ns
Antonelli et al. (25)	179	24% (initial thyroid status); 34% (last thyroid status)	179	12% (initial thyroid status); 16% (last thyroid status)	0.002 (initial thyroid status); <0.001 (last thyroid status)

AbTg, antithyroglobulin antibodies; AbTPO, antithyroperoxidase antibodies; F, female; FT4, free thyroxine; M, male; ns, not significant; OA, osteoarthritis; TSH, thyroid-stimulating hormone.

9/39 (23%) of SSc patients were hypothyroid, and 4/9 (44%) had positive ATA. Circulating AbTg and/or antimicrosomal antibodies were positive in 18% of the 39 patients.

A high prevalence of thyroid autoimmunity (15) was also observed in 43 Hungarian SSc patients. ATA were detected in 14 cases (33%) [4 cases with AbTg, 11 with antithyroperoxidase antibodies (AbTPO), and 5 with antimicrosomal antibodies].

Antithyroglobulin antibodies and AbTPO antibodies, FT3, FT4 and TSH, and HLA-DR typing were carried out in 85 SSc Italian patients (16). AbTg and AbTPO antibodies were detected in 12% (10/85) and 19% (16/85) of patients. Two patients with ATA had clinical hypothyroidism and shared the HLA-DR3 allele. A higher frequency of the HLA-DR15 was shown in SSc subjects in the presence of AbTPO antibodies than in patients without AbTPO.

Twenty-three female patients with SSc (mean age 37.7 ± 12.7) were evaluated for thyroid dysfunctions versus 15 normal females as controls (17). Mean serum levels of FT4 in SSc patients were significantly lower than in controls (7.46 ± 2.7 versus 10.47 ± 2.5). Of the 24 patients, 8 (33.3%) showed hypothyroidism (17).

Another Latin American study confirmed a high prevalence of thyroid autoantibodies in Brasilian patients with SSc (18).

In a large cohort study (19), 1,517 patients with rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), SSc, Sjögren's syndrome (SS), mixed connective tissue disease (MCTD), and polymyositis/dermatomyositis (PM/DM) were evaluated for thyroid dysfunctions clinically and by imaging and fine-needle aspiration cytology [with respect to prevalence of GD or Hashimoto's thyroiditis (HT) in the general population]. HT was more common among MCTD, SS, and RA patients (21, 7, and 6%, respectively) than GD (2.5, 3, and 1.6%, respectively). SLE, RA, SSc, MCTD, SS, and PM/DM had a higher prevalence for HT than the general population of 90-, 160-, 220-, 556-, 176-, and 69-fold, respectively, and for GD of 68-, 50-, 102-, 76-, 74-, and 37-fold, respectively.

A first study (20) aimed to assess the prevalence of thyroid disorders in SSc patients using a complete thyroid work-up, versus an internal appropriate control group. Two hundred two SSc patients versus 404 controls from the general population (matched by age and gender, with similar iodine intake) were evaluated for TSH, FT3, FT4, AbTg and AbTPO, thyroid ultrasonography and blood flow, and fine needle aspiration when needed. Odds ratios (OR) for female SSc versus controls subjects were significant for: clinical hypothyroidism, 14.5 (2.3–90.9); subclinical hypothyroidism, 3.2 (1.8–5.7); AbTPO positivity, 2.7 (1.8–4.1); thyroid hypoechoic pattern, 3.2 (2.2–4.7); thyroid autoimmunity, 3.7 (2.6–5.4); and thyroid volume <6 mL, 1.8 (1.2–2.7). OR for thyroid autoimmunity in male SSc patients versus control subjects was 10.8 (2.2–52.4). Female SSc patients had mean TSH levels significantly higher than control subjects, and female and male SSc patients had significantly higher AbTPO than controls. Three cases of GD in female SSc (versus zero in controls, $P < 0.05$), and two of papillary thyroid cancer (PTC) were reported in SSc patients.

The authors suggested to test thyroid function, AbTPO, and ultrasonography and to assess the clinical profile of SSc patients. Thyroid function follow-up (and appropriate treatments) should be performed periodically in women, subjects with positive AbTPO and hypoechoic and small thyroid.

The abovementioned results were confirmed in another study (21) that evaluated thyroid function and autoantibodies, in 79 SSc women, versus 81 age-matched women with osteoarthritis (OA) as controls. Hypothyroidism was found in 16 of 79 (20%) patients with SSc and in 9 of 81 (11%) patients with OA. AbTPO were present in 23% SSc versus 11% controls. The risk of hypothyroidism was significantly higher in AbTPO-positive patients ($P < 0.0001$).

A cross-sectional study (22) of two convenience samples of patients with SSc, one in Canada and the other in Colombia, was performed. Among 719 patients, 273 (38%) had at least one other autoimmune disease. Three hundred sixty-six autoimmune diseases were assessed, among which AITD (38%), RA (21%), SS (18%), and primary biliary cirrhosis (4%) were more frequent. Two hundred sixty patients (36%) had first-degree relatives with at least one autoimmune disease [RA (18%) and AITD (9%) were the most common]. These results suggest that polyautoimmunity is frequent in SSc patients and autoimmune diseases cluster within families of these patients.

To determine (23) the ATA prevalence in a large SSc cohort and to verify whether they are associated with distinct clinical phenotypes, 138 SSc patients (46 with dSSc and 92 with lSSc) and 100 healthy controls (HC) were tested for AbTg and AbTPO. A statistically significant increase of AbTPO was detected only in patients with lSSc compared to HC (32.6 versus 14%, $P = 0.003$).

Two hundred ten SSc patients were evaluated in a Japanese study (24), that identified 30 patients with AITD (14.3%), including 29 with HT (13.8%) and 1 with GD (0.5%).

A further study (25) first evaluated the incidence of new cases of clinical and subclinical thyroid dysfunction in SSc women versus controls from the same geographic area (matched by gender and age). SSc patients with thyroid dysfunction were excluded at the beginning, and then the manifestation of new cases of thyroid disorders was assessed in 179 patients and 179 matched controls, having a similar iodine intake (median follow-up: 94 months in controls; 73 months in SSc). An elevated incidence ($P < 0.05$) of new cases of hypothyroidism, thyroid dysfunction, AbTPO positivity, and hypoechoic thyroid, in SSc patients (15.5, 21, 11, and 14.6 of 1,000 patients per year; respectively) versus those in controls was observed. The onset of hypothyroidism was demonstrated (by logistic regression analysis) to be related to a borderline elevated initial TSH value, the presence of high AbTPO levels, and a hypoechoic and small thyroid in SSc patients.

A subsequent study (26) confirmed a high prevalence of subclinical hypothyroidism (8.5%), overt hypothyroidism (1.9%), subclinical hyperthyroidism (2.8%), and overt hyperthyroidism (0.9%) in SSc patients, and that a small thyroid volume (<4.5 ml) was related to hypothyroidism.

Positive ATA titers were also observed in 27/86 SSc Polish (27) patients (31%).

Recently, it has been also demonstrated that hypovitaminosis D was statistically associated with AT in SSc patients (28).

Conversely, a recent study (29) evaluated prospectively the prevalence of other autoimmune disorders in outpatient clinic in 3,069 consecutive patients with diagnosed chronic AT, with respect to two control groups (matched by age and gender): (a) a control group of 1,023 subjects, drawn out a random sample of the general

population without thyroid disorders and (b) 1,023 patients with non-toxic multinodular goiter extracted from the same random sample of the general population, with similar iodine intake. The results of the study demonstrated a significant increase of the prevalence of SSc in AT patients (with respect to both controls).

Different studies demonstrate elevated circulating CXCL10 (Th1) and CCL2 (Th2) chemokines in SSc patients of newly diagnosis. Patients with a serious clinical phenotype, including the involvement of lung and kidney, have higher CXCL10. CXCL10 declines during the follow-up, while CCL2 does not change, suggesting the progress from a beginning Th1 inflammatory stage to a successive Th2 phase (30, 31).

Th1 lymphocytes, interferon-γ, and interferon-γ-dependent chemokines (CXCL9, CXCL10, CXCL11) play a pivotal role in AITD, that are Th1 immune-mediated autoimmune disorders, too (32–35). Newly diagnosed SSc patients have elevated circulating levels of CXCL10, but not of CCL2, in the presence of AT, indicating a predominance of the Th1 immune response in these patients (36).

To sum up, the abovementioned data show a high incidence, and prevalence, of new cases of AT, and hypothyroidism, in patients with SSc, suggesting that in SSc women, with a borderline high (though in the normal range) TSH level, in the presence of AbTPO, and a hypoechoic and small thyroid, it could be necessary to monitor periodically thyroid function.

SSc AND GD

A first anectodal study reported an association of SSc and GD in three cases (37). One case of GD was also observed among 210 SSc Japanese patients (0.5%) (24). Graves' ophthalmopathy has been also occasionally reported in one SSc patient (38).

A significant number (3 cases) of GD in female SSc (3/202 versus 0/404 controls, $P < 0.05$) was also observed in a case control study (20), with an internal appropriate control group.

On the whole the abovementioned studies suggest a higher prevalence of GD in SSc patients; nevertheless further studies, involving a larger number of SSc patients, are necessary to confirm this finding.

SSc AND PTC

Single cases of PTC in association with SSc were reported in several studies (9, 20, 39–42).

However, more recently, the risk of TC in 327 unselected SSc patients with respect to two population-based, control groups was studied systematically (matched by age and gender; 654 subjects from an iodine-deficient area and 654 subjects from an iodine-sufficient area) (43).

Six subjects with PTC were detected among SSc patients, while only one case was observed in controls 1, as well in controls 2 ($P = 0.007$, for both). In SSc, all patients with TC showed thyroid autoimmunity versus 40% of the other SSc patients ($P = 0.001$) (43).

These findings suggest the possibility of a increased prevalence of PTC in SSc patients with thyroid autoimmunity, however, larger cohorts are needed to elucidate this.

CLINICAL ASPECTS OF SSc AND THYROID DISORDERS

Several studies have evaluated a possible association among thyroid disorders and clinical findings of SSc, reporting different results.

It was initially reported that patients with hypothyroidism had more frequently subcutaneous calcinosis (11).

Hungarian SSc patients with AbTPO concentration tended to have secondary SS (15).

In a further study in female patients with SSc (duration < 3 years), FT4 levels correlated significantly with Dlco% ($r = +0.90$, $P < 0.01$), while in patients with SSc duration > 3 years hypothyroidism correlated significantly with hand joint restriction of motion (17).

Seventeen SSc patients with high pulmonary systolic pressure (>35 mmHg) were studied in another article (44). High pulmonary pressure in these SSc patients was not associated with the type of SSc, or age; however, five SSc patients (12.5%) had alteration of the thyroid function (two cases of hypothyroidism, three of hyperthyroidism). The pulmonary pressure levels were higher in SSc patients with thyroid dysfunction, with respect to SSc in euthyroidism (40 versus 31 mmHg, respectively; $P < 0.05$). Furthermore, hypothyroid SSc patients had higher pressure levels, with respect to hyperthyroid SSc (46 versus 37 mmHg, respectively), even if not significantly. The lack of significant differences in pressure levels between hypothyroid, or hyperthyroid SSc, and the low frequency of ATA in pulmonary hypertension associated with SSc, suggest a vasomotor role of thyroid hormones, rather than an autoimmune mechanism (44).

In Japanese female SSc patients, the prevalence of anticentromere antibody positivity, SS, and severe facial skin sclerosis was significantly prevalent in the presence of AITD (24).

A study found a statistically significant increase of AbTPO only in patients with lSSc (but not in dSSc) compared to controls (32.6 versus 14%, $P = 0.003$) (23).

To sum up, most of the abovementioned studies did not observed any association among thyroid dysfunctions and/or autoimmunity and features of SSc (clinical or serological) (13, 20, 25, 27).

CONCLUSION

Many studies have shown a high incidence, and/or prevalence, of new cases of AT, and hypothyroidism in SSc patients, especially in the female gender. An association among a Th1 predominance, low levels of vitamin D, and AITDs has been also demonstrated in patients with SSc.

Few cases of GD have been also described in SSc patients, according with the higher prevalence of thyroid autoimmunity.

It has been also observed a higher prevalence of PTC, in association with AT, in SSc patients. However, in order to confirm results about GD and TC, studies in larger number of patients with SSc are needed.

To sum up, the abovementioned data strongly suggest that female SSc patients with a high risk (a borderline high though normal TSH value, the presence of AbTPO, and a hypoechoic

and small thyroid) should be periodically monitored for thyroid function, and appropriate treatments when needed.

AUTHOR CONTRIBUTIONS

PF, IR, DG, MC, SMF, AA, and CF gave substantial contribution in the conception and design of the work, and in writing the article. AA and CF revised it critically for important intellectual content. PF, IR, DG, MC, SMF, AA, and CF gave the final approval of the version to be published. PF, IR, DG, MC, SMF, AA, and CF agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Systemic Lupus Erythematosus and Thyroid Autoimmunity

Silvia Martina Ferrari[1], Giusy Elia[1], Camilla Virili[2], Marco Centanni[2], Alessandro Antonelli[1] and Poupak Fallahi[1]*

[1] Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy, [2] Department of Medico-Surgical Sciences and Biotechnologies, "Sapienza" University of Rome, Latina, Italy

Most of the studies present in the literature show a high prevalence, and incidence, of new cases of hypothyroidism and autoimmune thyroiditis (AT) in systemic lupus erythematosus (SLE) patients, overall in female gender. A limited number of cases of Graves' disease have been also reported in SLE patients, in agreement with the higher prevalence of thyroid autoimmunity. It has been also demonstrated that a Th1 predominance is associated with AT in SLE patients. Furthermore, a higher prevalence of papillary thyroid cancer has been recently reported in SLE, in particular in the presence of thyroid autoimmunity. However, studies in larger number of SLE patients are needed to confirm findings about thyroid cancer. On the whole, data from literature strongly suggest that female SLE patients, with a high risk (a normal but at the higher limit thyroid-stimulating hormone value, positive antithyroid peroxidase antibodies, a hypoechoic pattern, and small thyroid), should undergo periodic thyroid function follow-up, and appropriate treatments when needed. A careful thyroid monitoring would be opportune during the follow-up of these patients.

Keywords: systemic lupus erythematosus, autoimmune thyroiditis, hypothyroidism, Graves' disease, thyroid cancer, AbTPO, AbTg, CXCL10

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****Correspondence:***
Silvia Martina Ferrari
sm.ferrari@int.med.unipi.it

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INTRODUCTION

Systemic lupus erythematosus (SLE) is an autoimmune disease affecting mostly joints, skin, blood vessels, heart, lungs, kidneys, liver, and nervous system, in which the immune system attacks tissues and cells leading to inflammation and damage (1). The course of SLE is variable, with periods of exacerbation (called flares) alternating with periods of remission. SLE occurs nine times more often in the female gender than in male, and it is more frequent in people of non-European descent (1). Different types of autoantibodies are present in SLE patients (2). The difference of clinical features of SLE in different patients is due to the complexity of the risk factors (genetic, hormonal, and environmental), and the variety of circulating autoantibodies present (2, 3). Because of the presence of many different autoantibodies, SLE is classified as a "B-cell disease." Circulating blood lymphocytes in SLE patients show a Th2-like profile (4); however, Th1 lymphocytes and interferon (IFN)-γ have been demonstrated to be important for the immune pathogenesis of SLE (5). In fact, it has been shown that the

Abbreviations: AbM, antimicrosomal antibodies; AbTg, anti-thyroglobulin antibodies; AbTPO, antithyroid peroxidase antibodies; AH, autoimmune hypothyroidism; AITD, autoimmune thyroid disorders; AOR, adjusted odds ratio; APS, antiphospholipid syndrome; AT, autoimmune thyroiditis; ESS, euthyroid sick syndrome; GD, Graves' disease; IFN, interferon; IL, interleukin; OR, odds ratio; PTC, papillary thyroid cancer; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; SLEDAI, SLE disease activity; SS, Sjögren's syndrome; T4, thyroxine; T3, triiodothyronine; TBII, TSH-binding inhibitor immunoglobulin; ThyAb, thyroid autoantibodies; TNF, tumor necrosis factor; TSH, thyroid-stimulating hormone; TSI, thyroid-stimulating immunoglobulins.

assistance of the Th1 lymphocytes is necessary for the development of the disease, and in the absence of a functioning Th1 immune response "helpless" B cells are not functional enough to trigger SLE inflammation (6). Circulating autoantibodies, immune complex deposition, and complement activation are SLE hallmarks; however, a growing body of evidence has shown the importance of cytokines/chemokines in this disease, such as interleukin (IL)-6, B lymphocyte stimulator, IL-17, type I IFNs, tumor necrosis factor (TNF)-α, and Th1 chemokines. These cytokines/chemokines are important in the orchestration, maturation, differentiation, and activation of various immune competent cells, which mediate the local inflammation and produce the tissue injury.

Systemic lupus erythematosus is associated with many other autoimmune diseases, and autoimmune thyroid disorders (AITD) too (7, 8).

Here, we review the scientific literature about the association of SLE and AITD.

THE ASSOCIATION OF SLE AND AITD

After the initial case reports describing a coexistence of SLE and AITD, many systematic studies have evaluated the possible association of SLE and AITD (**Table 1**).

Prevalence of Thyroid Autoantibodies (ThyAb) in SLE Patients

Serological overlap among SLE, rheumatoid arthritis (RA), and AITD exists (9–12).

A first study evaluated thyroid disorders in 319 SLE patients showing 9 with thyrotoxicosis, 3 with hypothyroidism, and 2 with thyroiditis, suggesting a higher prevalence of thyroid disorders in SLE patients (13). Weetman and Walport compared the prevalence of ThyAb and abnormal thyroid-stimulating hormone (TSH) levels in 41 SLE patients, versus age- and sex-matched controls. A significant higher prevalence of ThyAb (51%) was observed in SLE compared to (27%) controls. Furthermore, hypothyroidism was observed in 10 SLE patients and 5 controls, usually in association with circulating ThyAb (14). In another study, 18% of SLE patients had positive antimicrosomal antibodies (AbM). Euthyroid sick syndrome (ESS) was diagnosed in 15% of SLE patients, and true or initial primary hypothyroidism in 5, and 39%, respectively. ThyAb were present in 45% of SLE patients with high TSH (15). Anti-TSH receptor antibodies were also evaluated in 28 SLE patients with thyroid disorders. 10/28 patients demonstrated thyroid-stimulating immunoglobulins (TSI) activity, while 5 patients had evidence of TSH-binding inhibitor immunoglobulin (TBII) activity. The TSI, or TBII activity, was not associated with

TABLE 1 | Prevalence of thyroid autoimmunity in SLE patients versus controls, in the studies that have an internal control matched by gender and age.

Reference	SLE patients (*n*)	AITD% in SLE patients	Controls (*n*)	AITD% in controls	*P*
Antonelli et al. (7)	213	Thyroid autoimmunity 34.7%	426	Thyroid autoimmunity 15.1%	<0.001
Antonelli et al. (8)	153	AbTg or AbTPO positivity 33%; AbTg and AbTPO positivity 12%	459 iodine-deficient controls and 459 iodine-sufficient controls	AbTg or AbTPO positivity 11% in iodine-deficient controls; AbTg or AbTPO positivity 13% in iodine-sufficient controls; AbTg and AbTPO positivity 2% in iodine-deficient controls; AbTg and AbTPO positivity 3% in iodine-sufficient controls	<0.0001 for AbTg or AbTPO positivity; 0.001 for AbTg and AbTPO positivity
Weetman and Walport (14)	41	ThyAb 51%	41	ThyAb 27%	<0.05
Vianna et al. (17)	100	ThyAb 21%; AbTg 11%	100	ThyAb 16%; AbTg 2%	0.009 for AbTg
Mihailova et al. (23)	12 children with SLE	AbTg 58%	27 children having juvenile chronic arthritis	AbTg 63% autoimmune thyroiditis 44.4%	Not reported
Shahin et al. (24)	45; AbTg and AbM were assessed in 27 patients	AbTg 18.5%	20	0	ns
Mader et al. (27)	77	AbTg 7.8%; AbTPO 5.2%	52	AbTg 7.7%; AbTPO 7.7%	ns
Appenzeller et al. (28)	524	Symptomatic AITD was observed in 6.1%	50	Symptomatic AITD was observed in 2%	>0.05
Lazúrová et al. (29)	80 patients with SLE or RA (12 SLE and 68 RA)	Prevalence of AITD 24%	34	Prevalence of AITD 8%	<0.05
Kumar et al. (30)	100	Prevalence of ThyAb 30%	100	Prevalence of ThyAb 10%	<0.05
Lin et al. (33)	1,633	Cumulative incidence of thyroid disease 8.1%	6,532	Cumulative incidence of thyroid disease 16.9%	<0.001

AbM, antimicrosomal antibodies; AITD, autoimmune thyroid disorders; AbTg, anti-thyroglobulin antibodies; AbTPO, anti-thyroperoxidase antibodies; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; ThyAb, thyroid autoantibodies.

the abnormal thyroid function tests (16). Vianna et al. studied 100 SLE patients for the presence of ThyAb and thyroid disease. The ThyAb were similar in SLE (21%) and controls (16%); AbTg were present in 11% SLE and only 2% controls; AbM levels were also different (median levels: SLE = 400; controls = 100). A higher frequency of clinical thyroid disease was observed in SLE patients with ThyAb (5/21; 3 hypothyroid, 2 hyperthyroid) than in those without (1/79). SLE patients with ThyAb were significantly older (mean age 47.5 years) than those without (mean age 37.5 years) (17). In a group of SLE female patients, thyroxine (T4) was significantly lower than in controls and 45.5% of patients with active SLE presented ThyAb. TSH basal, and after TRH stimulation, were significantly higher in patients with active SLE. ThyAb were not found in patients with inactive SLE (18). In 45 Chinese SLE patients, 24 (53.3%) had altered echographic findings. AbM and/or AbTg were reported in 21 patients (46.7%), and TBII in only one. Ten patients (22.2%) showed an altered thyroid function. Hashimoto's thyroiditis was reported in four patients (8.8%), two of whom had hypothyroidism. The mean disease duration was longer in patients with thyroid anomalies ($P < 0.05$) (19). Among 129 SLE patients from Singapore, 8.9% had hyperthyroidism, 3.9% Hashimoto's thyroiditis, and 47.8% ESS. AbM or AbTg were present in 32.2% (20). Kausman and Isenberg evaluated 150 SLE patients, showing that 31 (21%) were ThyAb positive. Follow-up data were available on 20 ThyAb positive patients (average of 7.9 years), of whom 12 (60%) were persistently ThyAb positive, while 8 (40%) were negative on at least one occasion during the follow-up. Five cases of clinical thyroid disease that were diagnosed, and 2/3 cases of subclinical elevation of TSH, occurred in the group with persistently positive ThyAb. Four (9%)/46 (among the 119) patients who initially were ThyAb negative, became ThyAb positive after a mean of 6.2 years; one had an elevated TSH (21). Among 37 SLE patients, positive anti-thyroperoxidase antibodies (AbTPO) were found in 11 (61%) of 18 patients with AbM, and in 3 (16%)/19 without (22). In 12 children with active SLE, aged 5–18 years, AbTg were positive in 7/12. The serum levels of triiodothyronine (T3), T4, and TSH were in the reference limits in all SLE children (23). Forty-five Egyptian SLE patients (43 women and 2 men) were evaluated for thyroid disorders, versus a group of 20 normal females. The mean serum free T3 levels in all patients were significantly lower than in controls (1.89 ± 1.14 versus 3.15 ± 0.93 pg/ml; $P < 0.05$), overall in patients treated with cyclophosphamide. Also serum free T4 levels in SLE patients were significantly lower than in controls. Two of 45 patients (4.4%) had primary hypothyroidism. The mean serum TSH levels in SLE patients were significantly higher than in controls (4.82 ± 22.2 versus 2.65 ± 1.18 μIU/ml; $P < 0.001$). Among six patients with decreased TSH levels, one showed decreased T3 and T4, two had decreased T4 only (24). In another study, the prevalences of HT, or Graves' disease (GD) in SLE patients, were 90-fold, and 68-fold, higher than in the general population (25).

Autoimmune thyroid disorders were evaluated in families with more than one SLE patient. Among 1,138 SLE patients, 169 had a diagnosis of Sjögren's syndrome (SS), of whom 50 (29.6%) also had AITD. Among the 939 patients with SLE without SS, 119 (12.7%) had AITD. Among 2,291 SLE-unaffected relatives, 44 had diagnosed primary SS and 16 (36.3%) of these also had autoimmune thyroid disease. 265/2,247 (11.8%) subjects had autoimmune thyroid disease. These findings suggested that autoimmune thyroid disease is observed in excess among SLE patients with a diagnosis of secondary SS, as among their SLE-unaffected relatives with a diagnosis of primary SS (26). Seventy-seven SLE patients were studied for thyroid disorders, against 52 controls. Hypothyroidism was reported in 11.6% of SLE patients compared to 1.9% of controls. None of the patients or controls had hyperthyroidism. No statistically significant difference was observed in the levels of anti-thyroglobulin antibodies (AbTg) or AbTPO between the study group and the control group. No association was found between the SLE disease activity (SLEDAI) score and the prevalence of ThyAb (27). In 524 patients with SLE, AITD were evaluated, versus 50 female adults. 32/524 (6.1%) SLE patients and 1/50 controls had symptomatic autoimmune thyroid dyfunctions, in particular hypothyroidism (28 SLE patients versus 1 control). Sixty (11.5%) SLE patients had subclinical thyroid diseases and 89/524 (17%) had positive ThyAb in absence of thyroid dysfunctions. ThyAb forerun the appearance of clinical autoimmune thyroid disease in 70% of SLE patients. SS and positive rheumatoid factor were more frequent in SLE patients with AITD than in those without. SLEDAI was correlated with the presence of hyperthyroidism (28). The prevalence of AITD in 80 patients with SLE or RA was significantly higher than in the 34 controls (24 versus 8%, $P < 0.05$) (29). Two hundred thirteen SLE patients were evaluated by assessing thyroid hormones, the presence of ThyAb, and thyroid ultrasonography with respect to 426 controls (matched by age and gender), from the same geographic area, with a well-defined status of iodine intake. In female SLE patients versus controls, the odds ratio (OR) was 4.5 [95% confidence interval (CI), 2.5–8.4] for subclinical hypothyroidism; 2.9 (95% CI, 2.0–4.4) for thyroid autoimmunity; and 2.6 (95% CI, 1.7–4.1) for AbTPO positivity. Female SLE patients had significantly ($P < 0.01$) higher mean values of TSH and AbTPO than controls, as a significantly ($P < 0.01$) higher prevalence of clinical hypothyroidism and GD. In this study, 3% of SLE patients had "non-thyroidal illness syndrome" versus 0 controls (7). Hundred SLE patients were also evaluated for AITD, in comparison with 100 controls (matched by sex and age). Thyroid dysfunction was reported in 36 (36%) (all women) SLE patients [14 (14%) with clinical hypothyroidism, 2 (2%) with subclinical hyperthyroidism, and 12 (12%) with subclinical hypothyroidism], versus 8 (8%) of controls. Eight patients (8%) had isolated low T3 in agreement with ESS. Eighteen (50%) of thyroid dysfunctions were of autoimmune origin with positive autoantibodies, but not the other 18 (50%). Twelve (12%) of SLE patients had elevated ThyAb alone, while only five (5%) of controls had primary hypothyroidism and three (3%) had subclinical hypothyroidism, and no cases of hyperthyroidism were reported. SLEDAI and thyroid dysfunction of sick euthyroid type were significantly associated. Prevalence of ThyAb in SLE patients was 30% with respect to 10% of controls. There were no other autoimmune endocrine diseases such as diabetes or Addison's disease in SLE patients (30). Among a total of 63 pregnant SLE women, 13% were on thyroid hormone prior to becoming pregnant, 11% were diagnosed with hypothyroidism during pregnancy, and 14% developed postpartum thyroiditis. The prevalence of preterm delivery was 67% in women with thyroid disease and 18% in women who were thyroid disease

free. The presence of ThyAb was not correlated with preterm delivery. This study suggests that pregnant women with SLE have an increased prevalence of thyroid disease. Women with SLE and thyroid disease have an increased prevalence of preterm delivery (31). The prevalence of thyroid diseases was retrospectively analyzed in 1,006 Chinese SLE patients. The prevalence of AITD was 2.78%, central hypothyroidism 1.29%, clinical hypothyroidism 1.69%, subclinical hypothyroidism 10.04%, hyperthyroidism 1.19%, ESS 9.54%, and nodules 1.09%, respectively. Subclinical hypothyroidism was more prevalent (10.04%) in this study, than the prevalence of thyroid abnormalities in the general Chinese population (0.91–6.05%). Moreover, patients with lupus nephritis had subclinical hypothyroidism more frequently (13.4%) than those without (7.3%, $P = 0.001$) (32).

However, discordant results have been recently reported (33). In 1,633 SLE patients of new diagnosis, the prevalence of hyperthyroidism, hypothyroidism, and autoimmune thyroiditis (AT) was compared with 6,532 controls (matched by sex and age). The cumulative incidence of thyroid disease in SLE patients was lower than in control subjects (8.1 versus 16.9%, $P < 0.001$). The authors suggested that SLE patients had a significantly lower rate of thyroid diseases and hyperthyroidism than matched controls (33). The reported study could have some limitations, able to affect the results, to be considered: (1) it was based on diagnostic codes released from The National Health Insurance Research Database, and for this reason details on thyroid serological assessments, presence of ThyAb, or SLE autoantibodies were not available; (2) data obtained in a retrospective cohort study are usually inferior in statistical quality to those derived from randomized trials because of the potential biases related to adjustments for confounding variables (33). A total of 376 Colombian SLE patients were evaluated for the presence of (1) confirmed autoimmune hypothyroidism (AH), (2) positive AbTPO/AbTg without hypothyroidism, (3) non-AH, and (4) SLE patients with neither. Confirmed AH prevalence was 12%. AbTg and AbTPO were reported in 10% and 21% euthyroid SLE patients, respectively. Patients with confirmed AH were significantly older and had later age at the onset of the disease. SS [adjusted OR (AOR) 23.2, 95% CI, 1.89–359.53, $P = 0.015$], smoking (AOR 6.93, 95% CI, 1.98–28.54, $P = 0.004$), and positive anticyclic citrullinated peptide (AOR 10.35, 95% CI, 1.04–121.26, $P = 0.047$) were associated with AH in SLE patients. Female gender, smoking, older age, SS, certain autoantibodies, and articular and cutaneous involvement were associated with this polyautoimmunity (34). Another meta-analysis evaluated the association of SLE and thyroid autoimmunity; a total of 1,076 SLE cases and 1,661 healthy controls were included. The meta-analysis results showed that the prevalence of ThyAb positivity in SLE patients was higher than in healthy controls (AbTg: OR = 2.99, 95% CI, 1.83–4.89; AbTPO: OR = 2.20, 95% CI, 1.27–3.82, respectively) (35). The frequency of AITD among 189 SLE patients was 6.3%, with 2.6% in the hyperthyroid group and 3.7% in the hypothyroid group. A new association between AITD and antiphospholipid syndrome was shown (36). Five thousand and eighteen patients with SLE and 25,090 age- and sex-matched controls were evaluated for thyroid dyfunctions. The proportion of hypothyroidism in SLE patients was increased with respect to the prevalence in controls (15.58 and 5.75%, respectively, $P < 0.001$). In a multivariate analysis, SLE was associated with hypothyroidism (OR = 2.644, 95% CI, 2.405–2.908) (37). Conversely, a recent study evaluated prospectively the prevalence of other autoimmune disorders in outpatient clinic in 3,069 consecutive patients with diagnosed chronic AT, versus two age- and sex-matched control groups: (a) a control group of 1,023 subjects, drawn from a random sample of the general population without thyroid disorders and (b) 1,023 patients with non-toxic multinodular goiter from the same random sample of the general population, with similar iodine intake. The results of the study demonstrated a significant increase of SLE prevalence in AT patients (versus both controls) (38).

Th1 and Th2 Cytokines in SLE

The ratios of Th1 and Th2 cytokines have been investigated to determine the cytokine homeostasis in SLE. Even if SLE was thought to be a Th2-polarized disease (39), more recently significantly elevated circulating cytokines of Th1 response, including TNF-α, and IFN-γ were also shown in SLE patients (40–42). Chemokine IFN-γ-inducible protein 10, the prototype of the chemokine (C-X-C motif) family, has chemotactic activity especially for activated Th1 cells and is involved in the pathogenesis of various Th1-dominant autoimmune diseases (43), and in SLE. Also AITD are Th1 immune-mediated autoimmune disorders in which Th1 lymphocytes, IFN-γ, and IFN-γ-dependent chemokines (CXCL9, CXCL10, CXCL11) play an important role (44–46). The common Th1 immune predominance in AITD and SLE should be the immunopathogenetic base of the association of these two diseases. On the whole, the abovementioned results show a high prevalence, and incidence, of new cases of hypothyroidism and AT in SLE patients, and suggest that female patients with systemic sclerosis, who are at high risk [a borderline high (even if in the normal range) TSH value, positive AbTPO, and a hypoechoic and small thyroid] should have periodic thyroid function follow-up.

THYROID ABNORMALITIES AND CLINICAL ASPECTS OF SLE

Many studies have tried to associate thyroid abnormalities with clinical findings of SLE, with different results.

An association between hypothyroidism, or AITD, and SLE clinical activity has been described in few studies (18, 28).

While another study found an association between SLEDAI score and ESS (30).

The reported data suggested that AITD is found more frequently among patients with SLE with a diagnosis of secondary SS, but not in SLE patients without SS (26, 28).

However most of the studies were not able to find any association among thyroid autoimmunity or thyroid dysfuntions, and clinical or serological features of SLE.

SLE AND PAPILLARY THYROID CANCER (PTC)

A first prospective study investigated the prevalence and features of thyroid cancer in 153 unselected SLE patients in comparison with two population-based, control groups (matched by sex and age): (1) 459 iodine-deficient controls and (2) 459 iodine-sufficient

controls. SLE patients had circulating TSH, AbTg and AbTPO levels significantly higher ($P < 0.001$ for all), and a higher prevalence of hypothyroidism ($P < 0.001$), than controls. Five PTC cases were reported in SLE patients, none in iodine-deficient controls ($P = 0.001$), and only one was shown in iodine-sufficient controls ($P = 0.001$). Thyroid autoimmunity was shown in 80% of SLE patients with confirmed thyroid cancer, and only in 31% of SLE patients without thyroid cancer ($P = 0.02$). These findings suggested that PTC prevalence in SLE patients is more elevated than in controls, especially in the presence of thyroid autoimmunity (8). Another study showed that among 16,409 patients [121,283 (average 7.4) person-years], 644 cases of cancer occurred, in particular hematologic ones, and a raised risk of thyroid cancer (SIR 1.76, 95% CI, 1.13–2.61) was observed too (47). A systematic review with meta-analysis investigated the risk of thyroid cancer in SLE revealing the positive association between thyroid cancer and SLE risk (48). A further meta-analysis assessed the association of SLE and malignancy evaluating 16 papers, including 59,662 SLE patients. The pooled relative risks were 1.28 (95% CI, 1.17–1.41) for overall cancer, 1.78 (95% CI, 1.35–2.33) for thyroid cancer (49). Also other studies confirmed the association between SLE and thyroid cancer (50).

CONCLUSION

Most of the studies show high prevalence, and incidence, of new cases of hypothyroidism and AT in SLE patients, overall in female gender. A limited number of GD cases have been also reported in SLE, in agreement with the higher prevalence of thyroid autoimmunity. It has been also demonstrated that Th1 predominance is associated with AT in SLE patients.

Furthermore, a higher prevalence of PTC has been recently reported in SLE patients, overall in the presence of thyroid autoimmunity. However, studies in larger number of SLE patients are needed to confirm data about thyroid cancer.

On the whole, data from literature strongly suggest that female SLE patients, with a high risk (a normal but at the higher limit TSH value, positive AbTPO, a hypoechoic pattern, and small thyroid) should undergo periodic thyroid function follow-up, and appropriate treatments when needed. However, studies in larger number of patients are required to evaluate if routine thyroid screening could be beneficial for SLE patients.

A careful thyroid monitoring would be opportune during the follow-up of these patients.

AUTHOR CONTRIBUTIONS

SMF, GE, CV, MC, AA, and PF gave substantial contribution in the conception and design of the work, and in writing the paper; gave the final approval of the version to be published; agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. MC, AA, and PF revised it critically for important intellectual content.

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Thyroid Autoimmunity and Antiphospholipid Syndrome: Not Such a Trivial Association

*Mathilde Versini**

Department of Internal Medicine, Archet-1 Hospital, University Hospital of Nice, Nice, France

Antiphospholipid syndrome (APS) is an autoimmune disease that manifests as recurrent venous or arterial thrombosis and/or pregnancy-related complications in the presence of persistent antiphospholipid (aPL) antibodies measured at least 3 months apart. APS occurs either as a primary condition or as a part of an underlying disorder, usually systemic lupus erythematosus (SLE). Otherwise, APS may be frequently associated with autoimmune disorders. Little is known about the association of APS and aPL antibodies with thyroid autoimmune diseases or thyroid autoantibodies. This is even more interesting that thyroid autoantibodies and aPL are both recognized causes of repeated miscarriages. Therefore, their combination is of particular importance in women of childbearing age. Several studies have pointed out an association between APS and thyroid autoimmunity, some of them suggesting common pathophysiologic processes and genetic background. A literature review was conducted on existing data on aPL/APS and thyroid autoimmune disorders, paying particular attention to the possible role of this association in obstetrical complications.

Keywords: antiphospholipid syndrome, autoimmunity, thyroid, Hashimoto's thyroiditis, Graves' disease, autoimmune disease

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Roberto Vita, University of Messina, Italy

***Correspondence:**
Mathilde Versini
versini.m@chu-nice.fr

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INTRODUCTION

Autoimmune thyroid diseases (AITD) encompass a spectrum of disorders characterized by a T-helper (Th)-1-cell-mediated autoimmune attack on the thyroid gland resulting in a lymphocytic infiltration of the thyroid parenchyma (1). AITD comprise two main presentations: Hashimoto's thyroiditis (HT) and Graves' disease (GD) corresponding to hypothyroidism and thyrotoxicosis, respectively.

The prevalence of AITD is estimated to be 5%, nevertheless the prevalence of antithyroid antibodies without clinical disorder may be even higher (1). HT (also named chronic autoimmune thyroiditis or autoimmune hypothyroidism) is the most common autoimmune disease with an incidence ranging from 27 to 448 per 100,000 per year according to the studies and the geographic areas (2), the most common endocrine disorder (3), as well as the most frequent cause of hypothyroidism (4). Its biological hallmark is the presence of antibodies directed to thyroid antigens, namely, thyroperoxydase (TPO) and thyroglobulin (Tg) (5). Similarly, GD is one of the most prevalent autoimmune

Abbreviations: AITD, autoimmune thyroid diseases; aPL, antiphospholipid; APS, antiphospholipid syndrome; GD, Graves' disease; HT, Hashimoto's thyroiditis; SLE, systemic lupus erythematosus; TAI, thyroid autoimmunity; Tg, thyroglobulin; Th, T-helper; TPO, thyroperoxydase; TSHR, thyroid-stimulating hormone receptor.

diseases with an annual incidence of about 14 per 100,000 and is associated with serum antithyroid stimulating hormone receptor antibodies (6).

Associations between thyroid autoimmunity (TAI) (AITD or isolated antithyroid antibodies positivity) and other organ-specific or systemic autoimmune disorders have been widely reported. Especially, type-1 diabetes, Addison's disease, vitiligo, alopecia, pernicious anemia, and celiac disease can be observed as part of type II or type III polyglandular autoimmune syndromes (1). Otherwise, TAI has been frequently reported in patients with systemic rheumatologic autoimmune conditions, such as systemic sclerosis (SS), Sjögren's syndrome, rheumatoid arthritis (RA), or systemic lupus erythematosus (SLE) (7).

Antiphospholipid syndrome (APS) is an autoimmune disorder associated venous or arterial thrombosis and/or pregnancy-related complications in the presence of persistent antiphospholipid (aPL) antibodies. APS occurs either as a primary condition or as a part of an underlying disease, usually SLE. Little is known about the association between APS and TAI. This is even more important considering that both antithyroid antibodies and aPL antibodies are major causes of recurrent miscarriage (RM).

Therefore, a literature review was conducted on existing data on the association of aPL antibodies/APS with AITD/TAI, paying particular attention to the possible role of this association in obstetrical complications.

ASSOCIATION BETWEEN TAI AND APS

Several case reports and small case series have investigated the presence of aPL antibodies in patients with AITD and the clinical significance of such an association (8–14) (reported in **Table 1**). The largest cohort is reported by Tektonidou et al. (14) who found a 12% prevalence of anticardiolipin (ACL) antibodies in 168 AITD patients compared with 0% in 75 healthy controls. Paggi et al. (11) and Nabriski et al. (12) found positive titers of aPL antibodies in 43% (ACL) and 54.8% (type not specified) of AITD patients, respectively (no control groups). Interestingly in Paggi's cohort (11), highest aPL levels were observed in GD patients with severe thyrotoxicosis and decreased following methimazole therapy. In Nabriski's survey (12), most aPL positive patients (86%) had IgG subtype. Marongiu et al. (8) found a 38% ACL positivity in 65 GD patients vs 0% in 58 controls. In HT, Osundeko et al. (13) observed a 21% prevalence of ACL antibodies. Conversely, two other studies (9, 10) failed to show a difference between patients and healthy controls.

Importantly, in all of these series none of the patients with positive aPL antibodies demonstrated APS manifestations. Rare case reports (15–20) describe patients presenting with concomitant GD and APS with thrombotic manifestations. There is no reported association of HT with thrombotic manifestations of APS. It is to note that GD has been implicated as a procoagulant state since many years, through several mechanisms including elevated factor VIII and fibrinogen levels, and increased factor X activity (21–23). Therefore, it is not surprising that the association of hypercoagulability inherent to the activity of GD and the presence of aPL antibodies may conduct to thrombotic manifestations. Apart from these rare cases, to date in the view of available data, aPL positivity during the course of AITD appear to be an epiphenomena without clinical impact. Indeed, aPL antibodies are often detected in patients with autoimmune disorders but the occurrence of clinical manifestations of APS remains scare.

Thus, such antibodies are presumed to result from an excessive stimulation of B lymphocyte clones with autoreactive potential (12). In addition, Hofbauer et al. (16) hypothesized a molecular mimicry between the epitopes of TSH receptors and β2 glycoprotein 1 as a possible pathogenic mechanism. Benvenga and Guarneri (24) explored this hypothesis through an *in silico* study and found homologies between various microorganisms

TABLE 1 | Association between TAI and APS.

Study	Number of subjects	Population	Antibody	Outcome
Marongiu et al. (8)	65 patients 58 controls	GD patients	ACL	Positive aPL in 38% of patients vs 0% of controls
Petri et al. (9)	52 patients 26 controls	GD (26) and HT (26) patients	ACL	No difference between patients and controls
Díez et al. (10)	69 patients 43 controls	AITD patients	ACL	No difference between patients and controls
Paggi et al. (11)	31 patients No controls	AITD patients	ACL	Positive aPL in 43% of patients
Nabriski et al. (12)	130 patients No controls	AITD patients	aPL (type not specified)	Positive aPL in 54.8% of patients
Osundeko et al. (13)	19 patients No controls	HT patients	ACL	Positive aPL in 21% of patients
Tektonidou et al. (14)	168 patients 75 controls	AITD patients	ACL	Positive aPL in 12% of patients vs 0% of controls
Innocencio et al. (26)	13 patients 163 controls	APS patients (not specified as primary or secondary) SS (25), RA (25), and healthy (113) controls	TgAb, TPOAb	No TAI positivity in APS patients
Mavragani et al. (27)	75 patients 150 controls	APS patients (40 primary, 35 APS secondary to SLE) SLE (75) and healthy (75) controls	TgAb, TPOAb	1. No significant difference between the 3 groups 2. SLE-APS have increased TPOAb 3. APS patients with TAI have more CNS involvement
de Carvalho and Caleiro (28)	50 patients No control	Primary APS patients	TgAb, TPOAb, TRAb	Positive TAI in 18% of patients
De Carolis et al. (29)	203 patients 162 controls	Primary obstetrical APS patients Controls with TAI and RM	TgAb, TPOAb	Positive TAI in 27% of APS patients

ACL, anticardiolipin; AITD, autoimmune thyroid diseases; aPL, antiphospholipid; APS, antiphospholipid syndrome; CNS, central nervous system; GD, Graves' disease; HT, Hashimoto's thyroiditis; RA, rheumatoid arthritis; RM, recurrent miscarriage; SLE, systemic lupus erythematosus; SS, systemic sclerosis; TAI, thyroid autoimmunity; TgAb, antithyroglobulin antibody; TPOAb, antithyroperoxydase antibody; TRAb, thyroid receptor antibody.

and thyroid antigens. Dagenais et al. (25) conducted an elegant immunogenetic study on family members with autoimmune diseases highlighting that HLA DR4 and DR7 antigens could predispose patients with GD and high titers of ACL antibodies to develop the full clinical spectrum of APS.

Few studies have investigated the relationship in the other direction, that is the prevalence of thyroid autoantibodies or AITD in APS patients (26–29) (reported in **Table 1**). In 2010, de Carvalho and Caleiro (28) evaluated the frequency of thyroid dysfunction and antibodies in 50 subjects with primary APS. Hypothyroidism was present in 22% of patients and thyroid autoantibodies in 18% of them. No clinical difference regarding thrombotic and obstetrical events was observed between APS patients with and without TAI. Mavragani et al. (27) tested 75 APS patients (40 primary APS and 35 APS secondary to SLE), 75 SLE patients and 75 healthy controls for anti-Tg and anti-TPO antibodies. No significant difference in the prevalence of thyroid antibodies was found between the three groups. However, SLE-APS patients (that is APS secondary to SLE) show significant increased rates of anti-TPO antibodies, but not primary APS patients, compared to healthy controls. More exciting is the fact that TAI identified a subgroup of APS patients with increased prevalence of ischemic central nervous system disease. Eighty-three percent of TAI-positive patients had evidence of central nervous system involvement vs 49% of TAI-negative patients. Authors speculated a cross-reactivity of these antibodies against shared epitopes between thyroid gland and central nervous system endothelium, such as α-enolase, an enzyme previously proposed to be involved in HT encephalopathy (30). Similarly, cross-reactivity between thyroid autoantibodies and CNS antigens had already been proposed by Le Donne et al. (31) to explain the neuropsychological perturbations observed in the postpartum. Innocencio et al. (26) were not able to replicate these results in a cohort of 63 patients including 25 RA, 25 SS, and 13 APS. None of the APS patients showed thyroid antibodies positive titers when compared with 13 and 8% of RA and SS subjects, respectively. In a large cohort of 203 women with primary obstetrical APS, De Carolis et al. (29) reported TAI in 27% of them. Of interest, as discussed later, patients with aPL antibodies alone had greater percentage of spontaneous pregnancies and live births when compared with patients positive for both thyroid antibodies and aPL antibodies.

On the basis of these data, it seems that the appearance of TAI in APS patients and conversely the occurrence of aPL in AITD patients is a fairly frequent phenomenon. The presence of aPL antibodies during thyroid disorders does not seem to have any clinical implication and more likely corresponds to hyper-stimulation of self-reactive B-clones. However, their occurrence during an active GD, the latter representing by itself a risk factor for thrombosis, may in rare cases lead to thrombotic manifestations. But studies remain scarce and small, larger cohorts will be needed to confirm these findings. In addition, in most studies, especially in older ones, only ACL antibodies were measured. Moreover, some important data are lacking to correctly interpret the clinical significance of these antibodies, in particular the levels of aPL antibodies and the eventual positivity for the lupus anticoagulant test.

APS, TAI, AND PREGNANCY

Although the association of aPL antibodies and antithyroid antibodies most often appears to have no clinical relevance, this may be of greater importance during pregnancy since both antibodies are recognized for their role in RM. RM is defined as three or more consecutive pregnancy losses with the same partner before 20 weeks of gestation (32). Etiologies include genetic, endocrine, anatomical, immunological, thrombophilic and environmental factors.

Antiphospholipid syndrome is the most important acquired risk factor for a treatable cause of recurrent pregnancy loss and can be found in 5–15% of cases (33). RM is part of APS clinical classification criteria (34, 35) that include vascular thrombosis and pregnancy morbidity. The latter criteria comprises: recurrent early miscarriage, late pregnancy loss, and prematurity due to placenta insufficiency or eclampsia/preeclampsia (35). Therefore, it is now widely accepted that aPL antibodies screening is an indispensable part of RM assessment. In addition, large randomized trials have allowed defining a standard of care based on antithrombotic treatment (36). Pathogenic mechanisms of pregnancy complications in APS are incompletely understood. aPL antibodies could reduce the proliferation and invasion of extra-villous trophoblasts, leading to placental mal-perfusion and finally to placental infarction, impaired spiral artery remodeling, decidual inflammation, increased syncytial knots and decreased vasculo-syncytial membranes (37).

Some endocrine disorders, such as diabetes mellitus, hyperprolactinemia and thyroid diseases have also been associated with miscarriage (38). The fact that overt hypothyroidism negatively affects pregnancy has been affirmed, but the implication of isolated TAI occurring in euthyroid women was still matter of debate. In 2011, Chen et al. (39) conducted a large meta-analysis including 22 studies: 14 cohort studies with 598 TAI-positive vs 4,870 TAI-negative pregnancies, and 8 case–control studies with 1,077 recurrent aborters. Overall, authors reported a significant higher risk of spontaneous miscarriage in euthyroid women with TAI (pooled OR = 2.55, $p = 0.002$ in case–control studies; pooled OR = 2.31, $p < 0001$ in cohort studies). The underlying mechanisms could consist of different aspects (39, 40): (A) heightened autoimmunity against foeto-placental unit, (B) direct involvement of thyroid autoantibodies interfering with trophoblast differentiation and proliferation, (C) induction of T-cell dysfunction causing an alteration of the endometrium that affects implantation, (D) higher age, and (E) mild hypothyroidism affecting reproductive outcome. Another hypothesis is that TAI may represent a marker for a global autoimmune state that is responsible for an elevated risk of reproductive failures rather than the actual cause of pregnancy losses. Anyway, as for aPL antibodies, the systematic search for TAI in women with RM is widely recommended (41).

Another important point to emphasize is that during pregnancy, GD may remain silent due to immune tolerance; But most often pregnancy and delivery can cause an onset and/or a flare-up of hyperthyroidism due to GD (42–44). The possible association with aPL antibodies is therefore important to consider since these antibodies may increase the thrombotic risk inherent in GD.

TABLE 2 | APS, TAI, and pregnancy.

Study	Number of subjects	Population	Antibody	Outcome
De Carolis et al. (29)	203 patients 162 controls	Primary obstetrical APS patients Controls with TAI and RM	TgAb, TPOAb, aPL (type not specified)	Positive TAI in 27% of APS patients Reduced fertility and worst pregnancy outcome in TAI+ and TAI/APS women when compared with APS alone women
Kim et al. (40)	256 patients	RM or unexplained infertility women	TgAb, TPOAb, aPL (6 types)	20% TAI positivity In TAI+ patients 27.8% ACL positivity vs 17.5% in TAI– patients
Promberger et al. (45)	156 patients	RM women	TgAb, TPOAb, ACL, β2GP1Ab	18% TAI positivity In TAI+ patients 13.8% aPL positivity vs 2.4% in TAI– patients No correlation with the number of miscarriages
Mecacci et al. (46)	69 patients 69 controls	RM, fetal death, or preeclampsia women	TgAb, TPOAb, ACL, LA	TAI higher in patients (37.9, 40.9, and 33.3%) vs controls (14.5%) No significant difference in aPL positivity

ACL, anticardiolipin; aPL, antiphospholipid; β2GP1Ab, anti-β2GP1 antibodies; LA, lupus anticoagulant; RM, repeated miscarriage; TAI, thyroid autoimmunity; TgAb, antithyroglobulin antibody; TPOAb, antithyroperoxydase antibody; APS, antiphospholipid syndrome.

Consequently, the combination of these two major factors, namely, aPL antibodies and antithyroid antibodies, could be of great importance for better understanding and management of RM. Main studies are reported in **Table 2**. Recently, Promberger et al. (45) evaluated the association between aPL antibodies and antithyroid antibodies in a large cohort of 156 women with RM. Eighteen percent of women had either anti-TPO or anti-Tg positivity. In women with positive antithyroid antibodies, 13.8% had aPL antibodies compared to 2.4% in TAI-negative women. Moreover, women with both anti-TPO and anti-Tg antibodies exhibited higher titers of aPL antibodies. Interestingly, none of the parameters of autoimmunity was correlated with the number of previous pregnancy losses (45). Kim et al. (40) reported in 265 women with RM or unexplained infertility a 20% prevalence of TAI. They observed an increased prevalence of ACL antibodies in TAI-positive women compared with TAI-negative patients (27.8 vs 17.5%, $p = 0.042$). In addition, they found higher Th1/Th2 cytokines-expressing CD3+/CD4+ T cells ratios in women with TAI, suggesting the implication of Th1 immunity and pro-inflammatory status in the pathogenesis of TAI-related RM. Mecacci et al. (46) evaluated the prevalence of thyroid autoantibodies in 69 women with RM, fetal death or preeclampsia and investigated their association with other autoantibodies. Antithyroid antibodies were present in 37.9, 40.9, and 33.3%, respectively, of patients, which was significantly higher than in healthy controls (14.5%). Unlike previous studies, the prevalence of aPL antibodies was no significantly different in women positive (26.9%) and negative (34.9%) for TAI.

But the most exciting trial to date on this topic was conducted by De Carolis et al. (29), to assess the presence of antithyroid antibodies in 203 women with primary obstetrical APS (aPL + RM) and compare APS alone with APS + TAI for fecundity and pregnancy outcome. It is to note that the type of aPL antibodies is not specified. A group of 162 women with TAI alone and RM served as controls. First, a 27% prevalence of TAI was found in APS subjects. Analyzing fecundity, 74% of APS-alone and 67% of total APS-positive women (APS alone and APS + TAI) became spontaneously pregnant, which was significantly higher than APS + TAI and TAI-alone women (48 and 49%, respectively). Therefore, women with TAI with or without APS had reduced fertility.

When pregnant, patients started a therapeutic regimen with high doses of intravenous immunoglobulin once a month until the 33rd week of pregnancy. Ninety-nine of the 136 pregnant women where thereafter followed. Pregnancy was successful for 92% of APS alone and 82% of total APS women, which once again was significantly higher than 60 and 57% in APS + TAI and TAI-alone women, respectively. In addition to reduced fecundity, TAI women had lower percentage of successful pregnancies. This study demonstrates the importance of TAI in patients with APS since it appears to be a stronger prognostic factor than aPL antibodies presence for fecundity and pregnancy outcome. Surprisingly, aPL and antithyroid antibodies do not seem to be synergic since rates are similar between TAI alone and TAI + APS groups. Authors conclude that TAI should always be evaluated in women with RM including those with aPL antibodies.

CONCLUSION

In the light of these data, the association of TAI and aPL antibodies appears to be quite common. In most cases, this phenomenon has no clinical consequence and is likely the result of hyperstimulation of self-reactive B-clones. However, rarely, the combination of an uncontrolled GD which is recognized as a factor of hypercoagulability and aPL antibodies may promote the occurrence of thrombotic events. This situation should therefore lead to greater attention. In addition, one study interestingly highlighted a possible relationship between central nervous system involvement and TAI/APS association. Further studies will be required to investigate this hypothesis. Finally, special attention should be paid to women of childbearing age. Indeed, the presence of aPL antibodies, isolated or in the context of an autoimmune disorder, but even more so of TAI even in the absence of thyroid dysfunction are major and independent factors of reduced fertility and worse pregnancy outcome. Screening should therefore include systematically these two elements, and the monitoring and management of the pregnancy should be adapted.

AUTHOR CONTRIBUTIONS

MV conducted the review and wrote the article.

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Sarcoidosis and Thyroid Autoimmunity

Piera Fazzi, Poupak Fallahi and Silvia Martina Ferrari*

Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy

Most of the studies have shown a higher risk for subclinical and clinical hypothyroidism, antithyroid autoantibodies [overall antithyroid peroxidase antibodies (TPOAb)], and in general, thyroid autoimmunity, overall in the female gender in patients with sarcoidosis (S). A significantly higher prevalence of clinical hypothyroidism and Graves' disease was also described in female S patients with respect to controls. Gallium-67 (Ga-67) scyntigraphy in S patients, in the case of thyroid uptake, suggests the presence of aggressive autoimmune thyroiditis and hypothyroidism. For this reason, ultrasonography and thyroid function should be done in the case of Ga-67 thyroid uptake. In conclusion, thyroid function, TPOAb measurement, and ultrasonography should be done to assess the clinical profile in female S patients, and the ones at high risk (female individuals, with TPOAb positivity, and hypoechoic and small thyroid) should have periodically thyroid function evaluations and suitable treatments.

Keywords: sarcoidosis, autoimmune thyroiditis, hypothyroidism, Graves' disease, antithyroid peroxidase antibodies, thyroglobulin antibodies

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****Correspondence:***
Poupak Fallahi
poupak@int.med.unipi.it

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INTRODUCTION

Sarcoidosis (S) is a systemic inflammatory disease distinguished by a huge accumulation of inflammatory cells, called granulomas, in multiple organs (1), overall in the lungs or its associated lymph nodes.

Though the cause of sarcoidosis is unknown (2), it seems to be provoked by an immune reaction to different triggers, as infections, or bacteria, dust, viruses, or chemicals. Generally, the body is protected by the immune system against foreign or dangerous substances, for example sending specific cells to protect organs. These cells secrete chemicals able to recruit other cells that can isolate and destroy such dangerous substance. Inflammation establishes during this process and stops as the foreign substance is removed. In S patients, the inflammation goes on even if the initial infection is eradicated (3). It often clears up by itself without the use of drugs, but in some cases, it goes on to affect the subject long term, and can be life-threatening requiring medications.

The onset of sarcoidosis is usually between 20 and 50 years of age and is more common in women. Subjects with a family history of sarcoidosis have an elevated risk to develop the disease.

It is sometimes asymptomatic and diagnosed not intentionally in almost 5% of cases. Fatigue, weight loss, lack of energy, dry eyes, joint aches, arthritis (14–38% of patients), swelling of the knees, shortness of breath, unclear vision, dry cough, or skin lesions are frequent symptoms, and in particular the cutaneous ones can be rashes, noduli, erythema nodosum, granuloma anulare, and lupus pernio (4–7).

Abbreviations: TPOAb, antithyroid peroxidase antibodies; AT, autoimmune thyroiditis; AITDs, autoimmune thyroid disorders; Ga-67, Gallium-67; HT, Hashimoto's thyroiditis; IL, interleukin; PGA, polyglandular autoimmune; S, sarcoidosis; T4, thyroxine; T3, triiodothyronine; TgAb, thyroglobulin antibodies; TSH, thyroid-stimulating hormone.

The collection of cells as macrophages, monocytes, and activated T lymphocytes is typical of granulomatous inflammation, during which an increased secretion of key inflammatory mediators, as tumor necrosis factor, interferon (IFN)-γ, interleukin (IL)-2, IL-8, IL-18, IL-12, and transforming growth factor-β is present, suggestive of a Th1-mediated immune response (8, 9).

Sarcoidosis is associated with autoimmunity such as autoimmune thyroid disorders (AITDs) (10, 11).

The Th1 chemokine IFN-γ-induced protein-10 is involved in the pathogenesis of this disease.

In this paper, we review the scientific literature about the possible association between sarcoidosis and thyroid autoimmunity.

THYROID AUTOIMMUNITY AND SARCOIDOSIS

Initially, some anectodal reports suggested a possible association between thyroid autoimmunity and sarcoidosis (**Table 1**) (12–15).

An association between sarcoidosis and hypothyroidism or hyperthyroidism was also suggested (16–19).

Later, Hugues et al. (20) evaluated the thyroid clinically, hormonally, and scintigraphically in 50 subjects with intrathoracic sarcoidosis. The patients were split in: T− 32 subjects, without thyroid abnormality; T+ 18 subjects, with thyroid disorders (2 thyroid nodules, 9 moderate diffuse goiters, 7 nodular goiters). All patients had normal triiodothyronine (T3), thyroxine (T4), and thyroid-stimulating hormone (TSH) levels, apart from 1 with Graves' disease. Few sarcoid granulomas were reported in 3/4 patients undergoing thyroidectomy. Activity, dissemination, type of sarcoid thoracic involvement were similar in the two groups. On the other hand, T+ patients had higher seric IgG levels than T− ($P < 0.05$). The authors suggested that autoimmune thyroiditis (AT) is not likely in these cases, in proportion to the low frequency of thyroid autoantibodies.

However, the association of AITD and sarcoidosis was suggested by other papers (21–24).

Papadopoulos et al. evaluated the frequency and type of endocrine autoimmunity in Swedish S patients (25). Among all the 89 patients with diagnosed sarcoidosis followed in the "Department of Pulmonary Medicine" from 1980 to 1991, 78 (34 females and 44 males; median age 48 years, range 22–81 years) were evaluated at the "Department of Endocrinology, Malmö University Hospital." 15/78 patients (19.2%) showed signs of endocrine autoimmunity clinically or serologically and two were affected by Addison's disease, with polyglandular autoimmune (PGA) syndrome type II. Thirteen patients had signs of thyroid autoimmunity, 8 with clinical AITD (6 with AT and 2 with Graves' disease; 2 with PGA syndrome type III, and 5 with isolated positivity of thyroid serology). One patient had premature ovarian failure and two insulin-dependent diabetes mellitus. Frequency of PGA syndrome type II, clinical AITD, and Addison's disease was significantly elevated with respect to the ones in the general population.

The authors concluded that a high frequency of endocrine autoimmunity was present in approximately 20% of S patients, the more frequent being PGA syndromes and thyroid autoimmunity.

Nakamura et al. (26) studied the incidence of thyroid autoantibodies and the prevalence of Hashimoto's thyroiditis (HT) in 62 patients with pulmonary sarcoidosis (diagnosed by clinical, radiographic and histological findings) and in three groups of controls with 40 and over years of age, without a known history of thyroid disease (88 hospital employees and 82 company workers, and 60 patients with pulmonary diseases other than sarcoidosis). Antibodies against antithyroid peroxidase (TPOAb) and purified thyroglobulin (TgAb) were tested by radioimmunoassay and

TABLE 1 | Prevalence of thyroid autoimmunity in patients with sarcoidosis versus controls, in the studies that have an internal control matched by gender and age.

Reference	Patients with sarcoidosis (*n*)	Autoimmune thyroid disorders (AITDs) % in patients with sarcoidosis	Controls (*n*)	AITD % in controls	*P*
Antonelli et al. (10)	F 75 M 36	50.7% 22.2%	F 225 M 108	35.1% 14.9%	0.0168 ns
Antonelli et al. (11)	30 patients with sarcoidosis with Ga-67 uptake	40%	54 patients with sarcoidosis without Ga-67 uptake	19%	0.03
Nakamura et al. (26)	62 patients with pulmonary sarcoidosis	17/62 (27.4%) had either positive TPOAb or TgAb or both	3 groups of subjects (see text)	In the 60 patients with pulmonary diseases, the overall prevalence was 8.3%; in the 88 hospital employees, the overall prevalence was 9.1%; in the 82 company workers, the overall prevalence was 8.5%	$P < 0.05$
Ilias et al. (27)	26 patients with active sarcoidosis	TgAb were slightly elevated in S patients, whereas TPOAb were within normal limits	26 patients with diagnosed chronic obstructive pulmonary disease		$P = 0.041$ for TgAb
Nowiński et al. (31)	557	13.1%	100	4%	0.0144
Wu et al. (33)	1,237	11.6%	4,948	7.3%	

TgAb, antithyroglobulin antibodies; TPOAb, antithyroid peroxidase antibodies; F, female; M, male; ns, not significant.

antibodies against microsomal antigen (MCHA) and thyroglobulin (TGHA) by hemagglutination.

17/62 patients (27.4%) had positive TPOAb or TgAb or both and were of middle or advanced age. Incidence of positive TPOAb/TgAb in S patients with 40 and over years age was 32.4% in females and 54.5% in males (37.8% overall). In the 60 patients with pulmonary diseases, 28 males (0%) and 5/32 females (15.6%) had positive TgAb and/or TPOAb, and the overall prevalence was 8.3%; in the 88 hospital employees, 1/45 males (2.2%) and 7/43 females (16.3%) had positive TPOAb/TgAb, resulting in a 9.1% of overall prevalence; in the 82 company workers, 5/65 males (7.7%) and 2/17 females (11.8%) had positive TPOAb/TgAb, the overall prevalence was 8.5%.

The prevalence was more elevated in S males with respect to control males matched by age (0–7.7% in the controls), and in S females was twice the one reported in controls (11.8–16.3%). Seven patients had HT, showing a prevalence of 11–3%, more elevated than previously reported.

A significantly higher incidence of thyroid autoantibodies in S patients of middle of advanced age, particularly in men, and a higher prevalence of HT, was shown than in previous papers.

Another study from Ilias et al. showed in 26 S patients (19 women and 7 men) that only TgAb autoantibodies were significantly elevated in these patients (27). TgAb were slightly elevated in S patients and differed significantly ($P = 0.041$) from controls (26 patients with diagnosed chronic obstructive pulmonary disease age- and sex-matched), whereas TPOAb levels were normal in all subjects and not significantly different between the two groups.

In a 26-year-old woman with systemic sarcoidosis a Gallium-67 (Ga-67), citrate scintigraphy showed an elevated radiotracer uptake in sarcoidal cutaneous lesions and in the thyroid (28), which could represent the sarcoidal involvement of the gland.

Isern et al. (29) reported that 10/348 (2.9%) S patients had AITD. Löfgren's syndrome was present in 8 patients; 3 subjects had Graves' disease, 6 HT with hypothyroidism, and 1 postpartum thyroiditis. In one patient, AITD had developed 15 years before sarcoidosis and in 9 subjects, it preceded the onset of AITD of about 4 months to 17 years. Among these, sarcoidosis was already present at the diagnosis of AITD. In one case, Graves' disease established as the patient was administered with potassium iodide to treat erythema nodosum. The authors concluded that sarcoidosis may be associated with AITD during its course, as hypothyroidism or hyperthyroidism.

Another study evaluated the prevalence of clinical and subclinical thyroid disorders in 111 S patients compared to 333 controls matched by age and gender from the same geographic area (10).

Thyroid hormones and antibodies, ultrasonography of the gland and fine-needle aspiration (FNA) were done.

The odds ratio (OR) for female S patients compared to controls was: for subclinical hypothyroidism, 2.7 [95% confidence interval (CI), 1.3–5.9]; for thyroid autoimmunity, 1.9 (95% CI, 1.1–3.2); for TPOAb positivity, 2.2 (95% CI, 1.2–3.9). TSH and TPOAb mean values were more elevated in S women than in controls ($P < 0.01$), as clinical hypothyroidism and Graves' disease ($P = 0.005$ and 0.0026, respectively), while no differences were reported for free T3 and T4, TgAb, thyroid volume and nodularity, and subclinical hyperthyroidism. Papillary thyroid cancer was shown in 2 S patients.

The authors concluded that thyroid function, TPOAb, and ultrasonography should be performed to evaluate the clinical profile in female S patients, and in the ones with an elevated risk (female individuals, with TPOAb positivity, and hypoechoic and small thyroid) thyroid function evaluations and suitable treatments should be performed periodically (10).

To assess the association of Ga-67 citrate thyroid uptake with thyroid disorders in S patients, 84 subjects were evaluated by ultrasonography, serum thyroid hormones and antithyroid antibodies, and FNA (11).

In S patients able to uptake Ga-67 compared to those not uptaking it, serum TSH, the titer of TPOAb and TgAb, and the prevalence of hypothyroidism or TgAb or TPOAb positivity were significantly higher; a hypoechogenicity of the thyroid was more recurrent. Thyroid nodules prevalence was similar in the two groups. Papillary thyroid cancer was reported in 2 S patients not uptaking Ga-67, and none with Ga-67 thyroid uptake.

The authors concluded that Ga-67 thyroid uptake is associated with aggressive AT and hypothyroidism in sarcoidosis, suggesting the evaluation of thyroid function and ultrasonography.

Martusewicz-Boros et al. (30) conducted a retrospective analysis assessing the incidence of comorbidity in 1,779 S patients (diagnosis code "ICD-10: D86") in Poland from 2008 to 2011.

About 79.2% had pulmonary and/or lymph node sarcoidosis (diagnosis code "D86.0, D86.1, D86.2"), 15.8% sarcoidosis of other and combined sites ("D86.8") and 5.0% unspecified ("D86.9"). Fifty-four percent of patients had at least one comorbid condition, overall arterial hypertension (22.4%), diabetes mellitus (5.0%), thyroid disorders (5.6%), obesity (3.3%), and chronic obstructive pulmonary disease (4.3%). Associations among the "number of comorbidities" and "age" and "extent of the disease" were shown ($P < 0.001$), by linear regression models. A comorbid condition was present more frequently in patients with multiorgan sarcoidosis.

Another study aimed to identify prevalence and frequency of comorbidities in S patients and to evaluate their influence on overall mortality (31).

Comorbidities and mortality were evaluated in a cohort of 557 S patients [291 men (52.2%) and 266 women (47.8%), mean age 48.4 ± 12.0 years] diagnosed from 2007 to 2011 and 100 control subjects [mean age (49.25 ± 10.3)].

The mean "number of comorbidities" in the two groups was similar (0.9 ± 0.99 versus 0.81 ± 0.84, not significant). Upon the diagnosis, thyroid diseases were significantly more frequent in S patients compared to control subjects (OR = 3.62; $P = 0.0144$). The median observation period was of 58.0 months, during which 16 patients died (2.9%). Non-survivors comorbidity was significantly higher than in survivors (2.8 ± 1.0, versus 0.8 ± 0.9; $P < 0.0001$).

The authors suggested that, in sarcoidosis, the comorbidity highly impacts mortality, and thyroid diseases are more common than in control subjects without sarcoidosis.

The prevalence of other autoimmune disorders in 3,069 consecutive outpatients with diagnosed chronic AT were assessed

compared to two control groups matched by age and sex: (a) 1,023 individuals, drawned out a random sample of the general population without thyroid disorders; (b) 1,023 subjects with non-toxic multinodular goiter from the same general population, with similar iodine intake (32). In AT patients, the prevalence of autoimmune disorders increased significantly compared to control subjects, for: sarcoidosis, polymialgia rheumatica, celiac disease, chronic autoimmune gastritis, vitiligo, rheumatoid arthritis, diabetes, multiple sclerosis, systemic lupus erythematosus, HCV-related cryoglobulinemia, Sjögren's disease, alopecia, psoriathic arthritis, and systemic sclerosis.

The association between sarcoidosis and autoimmune comorbidities was evaluated in 1,237 S patients and 4,948 controls matched by age and sex from the National Health Insurance Research Database from 1997 to 2010 in Taiwan, by multiple logistic regressions (33), showing a prevalence of sarcoidosis of 2.17/100,000 individuals. S patients had a higher risk of autoimmune comorbidities than controls (17.6% versus 9.4%, $P < 0.05$). Sarcoidosis was associated with AITD [adjusted odd ratio (aOR), 1.32; 95% CI, 1.05–1.64], Sjögren's syndrome (aOR, 11.6; 95% CI, 4.36–31.0), and ankylosing spondylitis (aOR, 3.80; 95% CI, 2.42–5.97). The sex-stratified analyses were performed and showed a significant association of sarcoidosis with ankylosing spondylitis in both sexes, with AITD in male patients and with Sjögren's syndrome in female patients, respectively, demonstrating that patients with sarcoidosis were inclined to have AITD, Sjögren's syndrome and ankylosing spondylitis, and the diagnosis of sarcoidosis usually preceded one of the associated comorbidities.

Moreover, cases of an uncommon involvement of the thyroid gland by sarcoidosis have been reported in literature. A paper by Cabibi et al. (34) reported the case of a 42 years old woman with sarcoidosis limited to the thyroid and adjacent small lymph nodes, without signs of systemic involvement or on other organs, showing thyroid nodules and normal biochemical levels and thyroid function parameters, and histologic sarcoid-type lesions, treated with thyroidectomy. Manchanda et al. (35) described the case of a man aged 54 years with asymptomatic non-toxic thyromegaly. He had an acute onset of dysphagia but the examination for gastrointestinal causes was negative. Chest imaging showed left-sided lymphadenopathy and biopsy of a lymph node showed sarcoidosis. Two years after, he had persistent dysphagia and underwent total thyroidectomy with resolution of dysphagia. Histopathological evaluation of the thyroid reported non-necrotizing granulomas in agreement with sarcoidosis. Furthermore, Papi et al. (36) reported two cases of patients with hyperthyroidism and histologically proven sarcoidosis.

CONCLUSION

Multiple endocrine gland insufficiencies are linked to other autoimmune and non-autoimmune diseases and such associations among different autoimmune diseases do not appear at random but in particular combinations; for example, AT is the pivotal disorder for type III PGA (37). Recently, a high prevalence of the association between rheumatic diseases (such as sarcoidosis, Sjögren's syndrome, mixed cryoglobulinemia, psoriathic arthritis, rheumatoid arthritis, systemic sclerosis, or systemic lupus erythematosus) and AITD has been demonstrated highlighting the possibility of a common pathogenic basis among them (32).

It has been hypothesized that the development of multiple autoimmunity could depend on shared epitope(s) between environmental agents and a common antigen in different endocrine tissues, and it has also been hypothesized that common specific germ layer antigens are expressed by the organs that took origin from the same germ layer, functioning as targets for autoimmune responses in PGA (37). Previous studies proposed that HLA-DQ genes, in particular DQA1*0102, could be a genetic marker for resistance to AITD, that is the most frequent disease in PGA type II or III. The paper by Wallaschofski et al. shows an association between DQA1*0301 and PGA type II or III, implying that the allele DQA1*0301 could be a marker of a higher risk for further PGA manifestations in patients suffering from an organ-specific autoimmune disease (38).

However, the precise pathogenetic mechanisms of multiple endocrine gland insufficiencies are not known (32).

As evidenced by immunopathological studies, a higher prevalence of Th1 immune profile is present in target organs of patients with Graves' ophthalmopathy, or chronic AT, or type 1 diabetes, at the onset of the disease (32). This higher prevalence at the beginning of autoimmune disorders, and the consequences of genetic and environmental conditions, could establish autoimmune phenomena in different organs in the same individual (32).

It is not clear if AT associated with other non-endocrine autoimmune disorders (NEADs) has a similar Th1 lymphocytes polarization.

In isolated HT or associated with NEAD, the paper by Santaguida et al. evaluated the intracellular Th1- and Th2-specific cytokines (39). A higher percentage of IL-2+ cells was shown in all subjects, with isolated HT or NEAD-associated. IFN-γ+ cells were increased in both groups, especially in the ones with HT + NEAD (19 versus 29.9%; $P = 0.0082$), while a higher number of IL-4+ cells was reported in 9.1% of patients with isolated HT and in 71% with HT + NEAD ($P < 0.0001$; relative risk = 3.18). Patients with NEAD-associated AT are characterized by a well-defined increase of IL-4+ lymphocytes. This could represent an initial tool to detect patients with AT in whom additional NEAD may be foreseen (39).

Most of the studies have shown in patients with sarcoidosis a higher risk for subclinical and clinical hypothyroidism, antithyroid autoantibodies, and overall TPOAb, and in general, thyroid autoimmunity, particularly in the female gender. A significantly higher prevalence of clinical hypothyroidism and Graves' disease was also shown in female S patients than in controls.

Ga-67 scyntigraphy in S patients when associated with thyroid uptake suggests the presence of aggressive AT and hypothyroidism. For this reason, thyroid function and ultrasound should be done in the case of Ga-67 thyroid uptake.

Sarcoidosis is one of the several associated autoimmune disorders included in PGA type III (32). AITDs are very prevalent

while sarcoidosis is quite rare; for this reason, it is not necessary to look for sarcoidosis in patients with AITD but is mandatory to screen thyroid autoimmunity in patients with sarcoidosis.

In conclusion, thyroid function, TPOAb, and ultrasonography should be performed to evaluate the clinical profile in female patients with sarcoidosis; the ones with high risk (female individuals, with TPOAb positivity, and hypoechoic and small thyroid) should have periodically thyroid function evaluations and suitable treatments.

AUTHOR CONTRIBUTIONS

PIF, PF, and SMF gave substantial contribution in the conception and design of the work, and in writing the paper. PF and SMF revised it critically for important intellectual content. PIF, PF, and SMF gave the final approval of the version to be published. PIF, PF, and SMF agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Autoimmune/Inflammatory Syndrome Induced by Adjuvants and Thyroid Autoimmunity

*Abdulla Watad[1,2,3], Paula David[2,4], Stav Brown[3] and Yehuda Shoenfeld[2,3,5]**

[1] Department of Medicine "B", Sheba Medical Center, Tel-Aviv, Israel, [2] Zabludowicz Center for Autoimmune Diseases, Sheba Medical Center, Tel-Aviv, Israel, [3] Sackler Faculty of Medicine, Tel-Aviv University, Tel-Aviv, Israel, [4] Faculdade de Ciências Médicas, Universidade do Estado do Rio de Janeiro, Rio de Janeiro, Brazil, [5] Laura Schwarz-Kipp Chair for Research of Autoimmune Diseases, Tel-Aviv University, Tel-Aviv, Israel

The autoimmune/inflammatory syndrome induced by adjuvants (ASIA), presented by Shoenfeld and Agmon-Levin in 2011, is an entity that incorporates diverse autoimmune conditions induced by the exposure to various adjuvants. Adjuvants are agents that entail the capability to induce immune reactions. Adjuvants are found in many vaccines and used mainly to increase the response to vaccination in the general population. Silicone has also been reported to be able to induce diverse immune reactions. Clinical cases and series of heterogeneous autoimmune conditions including systemic sclerosis, systemic lupus erythematosus, and rheumatoid arthritis have been reported to be induced by several adjuvants. However, only a small number of cases of autoimmune thyroid disorder have been included under the umbrella of ASIA syndrome. Indeed, clinical cases of Hashimoto's thyroiditis and/or subacute thyroiditis were observed after the exposure to vaccines as well as silicone implantation. In our review, we aimed to summarize the current knowledge on ASIA syndrome presented as endocrinopathies, focusing on autoimmune thyroid disorders associated with the various adjuvants.

Keywords: autoimmune/inflammatory syndrome induced by adjuvants, thyroid, endocrinopathy, adjuvants, vaccines, silicone, Hashimoto's thyroiditis, Graves disease

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****Correspondence:***
Yehuda Shoenfeld
shoenfel@post.tau.ac.il

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INTRODUCTION

Adjuvants are substances that are able to trigger autoimmunity *via* a variety of mechanisms, such as alteration of the host's immune system, polyclonal activation of B cells, effects on cellular immunity, immunoregulatory cells, viral-induced antibodies, and acceleration of molecular mimicry (1). Exposure to adjuvants can occur in a variety of methods due to their wide range of uses in vaccines, mineral oils, silicone implants, and many other products and devices. The association between adjuvant exposure and autoimmunity manifests itself in five autoimmune conditions sharing similar autoimmunity manifestations (2, 3), such as the postvaccination phenomena, the macrophagic myofasciitis syndrome (MMF), the Gulf war syndrome (GWS), siliconosis, and the sick building syndrome (SBS) (4, 5). The autoimmune/inflammatory syndrome induced by adjuvants (ASIA), presented by Shoenfeld and Agmon-Levin (6) in 2011, is a single entity that incorporates all five conditions. Extensive research has identified the genetic background, contributing to the development of ASIA syndrome in predisposed individuals following adjuvant exposure. A large number of autoimmune diseases share several alleles of the HLA class II such as DRB1 locus. The development

of specific autoantibodies is determined by DRB1 alleles leading to an abnormal response and development of full-blown autoimmune diseases (7, 8).

When used in vaccines, adjuvants are purposely used as immunogenicity enhancing agents that are essential for directing the adaptive immunoresponse (9). However, they might also trigger undesired autoimmune reactions that question the use of adjuvants and their safety in the context of DRB1*01 genetic background (10).

A systematic review by Jara et al. (4) reported that 4479 ASIA cases have been identified since its presentation in 2011. Among them, 305 were considered severe, with the majority of these cases being developed following vaccines mainly directed to HPV, HBV, and seasonal influenza. Despite vaccines' proven record of safety and efficiency, aluminum hydroxide was used in these vaccines along with the viral antigens as an adjuvant. Due to aluminum's capability to enhance the immunoresponse, it enables the usage of smaller amount of antigens. However, enhanced immunogenicity might lead to enhanced reactogenicity in a process not always benign involving pathological stimulation (11).

The other adjuvants containing products yielding severe clinical manifestations are silicone implants and mineral oil fillers (4, 12).

Silicone has been considered as an inert material, which is unable to induce immune reactions in the human body. Therefore, it has been used in many medical devices for the last 60 years, including both silicone and saline breast implants. However, a possible association between silicone exposure and autoimmune diseases has been reported in many studies demonstrating the development of autoimmune diseases and autoantibodies in patients following exposure to silicone implants (13, 14). Improved clinical manifestations after the extraction of implants (15) support the relationship between silicone and autoimmunity.

Mineral oil injections, which are prevalent in Mexico and Latin America for cosmetic uses, have been identified as a leading cause of ASIA syndrome as well *via* the proposed mechanism of chronic inflammation induction leading to granuloma formation and thickening of the dermis (4, 10).

The risk for autoimmune diseases, determined by the patient's genetic background, is increased in patients with autoimmune diseases history such as type 1 diabetes mellitus (T1DM). Thyroid antibodies can be identified in approximately 20–25% of patients with type 1 diabetes, and up to 50% of them progress to clinical autoimmune thyroid disease (AITD) (16). Thyroid autoimmune diseases have been described in many case reports and case series, presenting thyroid autoimmune manifestations along with other autoimmune conditions.

In genetically predisposed individuals, under particular conditions, molecular mimicry between microbial and human antigens has been shown to be able to turn a defensive immunoresponse into autoimmune response. This mechanism has yet to be explored in the field of thyroid autoimmune diseases (17). In our review, we aimed to summarize the current knowledge about ASIA syndrome and the relationship between adjuvants and autoimmune diseases, focusing on its association with autoimmune endocrinopathies and thyroid autoimmunity.

ENDOCRINOPATHY AND ASIA SYNDROME

Pathological processes of the endocrine glands result in abnormal levels of circulating hormones, which lead to endocrinopathies. Some endocrine disorders are immune mediated, such as Hashimoto's thyroiditis (HT), Graves' disease, and T1DM (18–20). Thus, it is possible that endocrine autoimmune diseases can be triggered by adjuvants, configuring cases of ASIA syndrome. Case reports, cohort and case–control studies on ASIA syndrome, and the majority of the endocrinopathies are still scarce. Lately, primary ovarian failure (POF) has been linked to ASIA, especially after vaccination (21–25).

Primary ovarian failure or premature ovarian insufficiency is defined as a combination of amenorrhea, for a minimum of 4 months, decline in sex steroids, and follicle-stimulating hormone (FSH) above 40 IU/l at two measurements with an interval of at least 1 month in women younger than 40 years (26). POF is a disorder with multiple etiologic mechanisms. The presence of lymphocytic invasion in the oophorus and the identification of autoantibodies against ovarium antigens on the theca, granulose, corpus luteum, and zona pellucida (27–29) support the idea that part of its etiology, estimated in 20–30% (30), is immune mediated. Furthermore, POF is commonly associated with other autoimmune diseases, including Addison's disease, thyroiditis, autoimmune polyglandular syndrome, systemic lupus erythematosus (SLE), hemolytic anemia, idiopathic thrombocytopenic purpura (ITP), and Sjogren's syndrome (31). The pathogenesis of POF also involves genetic mutations, metabolic disorders, and environmental factors, such as virus infection, chemo and radiotherapy, and surgeries (30).

HPV vaccine has been reported as an important issue in ASIA syndrome, already being related, for instance, to Guillain-Barré syndrome and other neuropathies, such as SLE, vasculitis, ITP, and autoimmune hepatitis (32–36). Developing autoimmune diseases as an adverse effect of the vaccine can be both due to its HPV virus-like particles, which have potent immuno-stimulatory properties (and can induce autoimmunity by molecular mimicry, epitope spreading, bystander activation, and polyclonal activation) (37), and due to the presence of aluminum as an adjuvant in the vaccine (38). Adjuvants are capable of increasing, intensifying, and prolonging antigen-specific immunoresponse of the vaccines without holding its own specific antigenic effect (38). Autoimmune well-defined diseases, as well as the non-specific immune disorders, following vaccination can present as a subacute vaccination side effect or appear months or years after the boosters (39–43). Genetically predisposed patients are more likely to exhibit late manifestations and are in a higher risk of developing ASIA syndrome (36, 44).

Colafrancesco et al. (21) recently reported three cases of POF following immunization with HPV vaccine. The three patients fulfilled the criteria for ASIA syndrome suggested by Shoenfeld and Agmon-Levin (6). They described three young women, previously healthy and with normal sexual development, who received three administrations of the quadrivalent HPV vaccine. The patients experienced general symptoms, including nausea, stomachaches, heavy and burning sensations in the injected arm,

headaches, insomnia, arthralgia, depression, anxiety, and difficulty in concentrating, and then presented amenorrhea within approximately 10 months, 2 years, and 10 years after the first dose. Two of them were positive for previously negative antibodies (anti-TPO and antiovarian). Hormonal screening was performed, showing increased FSH and luteinizing hormone (LH) plus extremely low levels of estradiol. Pregnancy was excluded, as well as no abnormalities were revealed in the transvaginal and pelvic ultrasound. After a karyotype evaluation and search for Fragile X syndrome with no aberrations, they were diagnosed with POF. Moreover, two of the three patients were siblings leading to the hypothesis that may exist as a rare risk factor for this adverse effect.

Little and Ward (22) also reported a case of POF succeeding HPV vaccination, in a 16-year-old patient, who presented irregular menses after taking the quadrivalent vaccine, followed by oligomenorrhea and amenorrhea. Her hormone profile also showed high levels of FSH and LH and low levels of estradiol and anti-mullerian hormone (AMH), and after excluding pregnancy and genetic, endocrinal, and other causes, she was diagnosed with POF.

Problems of quadrivalent HPV vaccine introduction in the market were wisely pointed by Little and Ward (25). They reported three other cases of young women who develop POF after having quadrivalent HPV vaccine and questioned some issues about its safety. First, despite the fact that the vaccine protocol suggests three doses, in the preclinical studies for toxicity, only two boosters were given to the rats. Still, the animals' reproductive system was not analyzed in a long-term period. Moreover, the phase II and III clinical studies on safety of the vaccine regarding the fertility were not complete: half of the subjects studied were lost to follow-up at 1 year; some of the subjects were on hormone contraception methods, which could mask the ovarian insufficiency; they have not considered medical conditions that flourished more than 7 months after the vaccination as associated with the vaccine; and adverse effects were only reported 2 weeks after the boosters. Furthermore, the placebo used as control in the phase III safety studies of the quadrivalent HPV vaccine was aluminum, also present in the vaccine solution, which was already shown to play as an adjuvant in ASIA syndrome.

Thus, HPV vaccine is likely to be an important trigger in ASIA syndrome, including immuno-mediated endocrine disorders, such as POF. Due to long periods of intervals between the vaccine injections and the development of the ovarian insufficiency, it is questionable if there is indeed a causal relationship between them. However, as previously mentioned, the safety preclinical and clinical studies of HPV vaccine are lacking some information regarding fertility safety, and the side effects were shown to be able to appear even after months or years.

Other vaccines and adjuvants may also trigger POF, as well as other immuno-mediated endocrinopathies, like for instance, type 1-diabetes may be induced by the same adjuvants. Indeed, in a cohort study with 211 young female patients with autoimmune diseases and 857 matched controls, they showed that patients exposed to quadrivalent HPV vaccine were in a higher risk of developing type 1-diabetes mellitus (OR = 1.2) (45). Additionally, it was shown in a prospective cohort study (46) that some vaccines are related to increased levels of diabetes autoantibodies, such as antibody against glutamic acid decarboxylase (GADA) and tyrosine phosphatase (IA-2A). These autoantibodies, which are considered reliable markers for the disease process (47, 48), were more frequently found in the subjects who received hemophilus influenza B (HIB) vaccination (OR = 5.9 and 3.4 in IA-2A and GADA, respectively). Especially, the IA-2A serum concentrations were significantly higher in patients exposed to HIB. Also, BCG was correlated to an enhanced prevalence of IA-2A ($p < 0.01$). The previously mentioned studies suggest that ASIA syndrome, particularly post vaccination, and endocrinopathies might be linked.

AUTOIMMUNE THYROID DISEASE AND ASIA SYNDROME

During the last years, abundant case reports and series were published supporting that various autoimmune disorders may be induced by adjuvants and be enclosed under ASIA syndrome (4, 12). Despite the fact of being the most common autoimmune disorder, unexpectedly, we have revealed very few articles and case reports in the literature describing the induction of AITD by various adjuvants. In this section, we report that the relevant case descriptions of AITD were reported to be correlated to immunization and silicone implants.

Hernàn Martinez et al. (49) described a case of a 55-year-old man with a family history of autoimmune diseases and medical history of diabetes and psoriasis, who developed subacute thyroiditis shortly after the administration of an influenza vaccine. Subacute thyroiditis is a very rare disease, and the authors of the mentioned case concluded that the induction of the disease was a result of an interaction between the genetic predisposition and vaccination. Another similar case of subacute thyroiditis was reported in a 25-year-old female (50). The patient was admitted due to fever, swelling, and tender mass in the neck. Two days before her presentation, she received influenza vaccine (Vaxigrip). Biopsy of the thyroid has revealed multinuclear giant cell granulomas.

A previously healthy 36-year-old female presented with clinical symptoms of thyrotoxicosis including tachycardia, anxiety, and tenderness in her neck (51). One month before her presentation, she received H1N1 vaccine. Thyroid function tests confirmed remarkable thyrotoxicosis. Thyroid scintigraphy was performed and showed significant diffuse reduction in the technetium uptake. Therefore, a diagnosis of subacute thyroiditis was made. Moving to another type of adjuvant, cases of granulomatous inflammation of the thyroid have been reported with silicone breast implants (52). Vayssairat et al. (53) described two cases of HT after receiving a silicone gel-filled breast implants. Both cases were induced after a long period of incubation, the first case is a 45-year-old women who had bilateral silicone implant of the breast in 1976 and developed HT in 1991. In addition, the patient complained of other non-specific symptoms including fatigue, morning stiffness, and sicca syndrome. Thyroid ultrasonography

showed an enlarged thyroid gland with a diffusely hypoechogenic pattern. The implants were painful and removed, showing extremely dense connective tissue with fibrosis. The second case of HT presented with hyperthyroidism clinical manifestation, 10 years after the silicon implantation, reporting positive anti-TPO. The implants were again painful, and the patient developed positive antinuclear antibodies (ANA). An animal experiment aimed to evaluate the immunological adjuvancy potential of silicone gel taken from breast implants (54). The study has found that silicone gel is able to stimulate the production of autoantibodies to rat thyroglobulin and bovine collagen II. However, this immune reaction was not associated with any histological evidence of thyroiditis or arthritis.

A cohort study was performed to assess the risk of new onset autoimmune disease in young women exposed to human papillomavirus-16/18 AS04-adjuvanted vaccine in the United Kingdom (55). The study reported an incidence rate ratio (95% CI) of 3.75 (1.25–11.31) for autoimmune thyroiditis among females.

An animal study has reported that immunization of BALB/c mice with the extracellular domain of the human TSH receptor led to the production of TSH binding-inhibiting and thyroid-blocking antibodies accompanied by lymphocytic infiltration of the thyroid (56).

In summary, ASIA syndrome is being more recognized by physicians, and therefore, more studies and cases have reported the correlation of the exposure to various adjuvants with diverse autoimmune diseases. Still, very few clinical reports and animal models studies were published to show the relationship between endocrinopathies in general and AITD in particular with adjuvants. However, the clinical cases of HT and/or subacute thyroiditis were observed after the exposure to vaccines as well as silicone implantation. Therefore, we believe that the minority of cases is not owing to rarity of association between adjuvants and AITD rather than the lack of awareness among physicians of such association. Consequently, physicians must be mindful that thyroiditis and other thyroid disorders can be induced by diverse adjuvants and therefore to reconsider non-essential vaccination in genetically predisposed individuals for autoimmune diseases.

AUTHOR CONTRIBUTIONS

AW, PD, SB, and YS designed the study and reviewed the literature on ASIA syndrome and thyroid autoimmunity. AW, PD, and SB wrote the manuscript. AW and YS edited the manuscript. All the authors have revised the paper and approved the final edition.

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Thyroid Autoimmunity and Function after Treatment with Biological Antirheumatic Agents in Rheumatoid Arthritis

*Sofie Bliddal†, Stina Willemoes Borresen† and Ulla Feldt-Rasmussen**

Department of Medical Endocrinology, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark

With the increased pro-inflammatory response in both rheumatoid arthritis and thyroid autoimmune diseases, treatment with biological antirheumatic agents (BAAs) of the former may affect the course of the latter. In hepatitis C and cancer patients, treatment with biological agents substantially increases the risk of developing thyroid autoimmunity. As the use of BAAs in the treatment of rheumatoid arthritis is increasing, this review aimed to investigate if such use affected thyroid status in rheumatoid arthritis patients. We conducted a systematic literature search and included six studies with a total of 311 patients as well as three case reports. The patients were treated with tumor necrosis factor-α inhibitors (infliximab, etanercept, or adalimumab) or the monoclonal CD20-antibody rituximab. There was a non-significant trend of slight improvement of both thyroid function and autoantibody status: a reduction of thyroid peroxidase and thyroglobulin antibody concentrations, and a reduction of thyrotropin levels in hypothyroid patients. Despite the small number of studies, they presented compliant data. The BAAs used in rheumatoid arthritis thus did not seem to negatively affect thyroid status in patients with rheumatoid arthritis and can be considered safe with regard to thyroid autoimmunity. However, the well-established association between rheumatic diseases and thyroid autoimmunity necessitates continued monitoring of thyroid function in patients with rheumatoid arthritis. Each new BAA should be scrutinized for its effect on thyroid as well as other autoimmune diseases in order to establish concise recommendations for patient follow-up for each agent and each disease.

Keywords: autoimmune thyroiditis, rheumatoid arthritis, biological antirheumatic agents, Hashimoto's thyroiditis, Graves' disease, thyroperoxidase antibody, thyroglobulin antibody, tumor necrosis factor-alpha inhibitors

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****Correspondence:***
Ulla Feldt-Rasmussen
ufeldt@rh.dk

†These authors have shared first authorship.

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INTRODUCTION

Autoimmune thyroid diseases are the most common autoimmune diseases and are often associated with the presence of other organ-specific or non-organ-specific autoimmune diseases (1). The coexistence of thyroid autoimmunity and rheumatoid arthritis has been acknowledged for over a century (2). Population studies have confirmed an increased prevalence of autoimmune thyroid disease in patients with rheumatoid arthritis and conversely, an increased prevalence of rheumatoid arthritis in patients with autoimmune thyroid disease (3, 4). Boelaert et al. (5) asked 3,286 thyroid patients to report other autoimmune diagnoses among themselves and their relatives. Rheumatoid arthritis was the most prevalent coexisting autoimmune disease occurring in

3.15% of patients with Graves' disease and 4.24% of patients with Hashimoto's thyroiditis (5). Similarly, Fallahi et al. (6) found a 2.4% prevalence of rheumatoid arthritis in 3,069 patients with verified autoimmune thyroiditis, which was significantly higher than in patients with multinodular goiter and in thyroid-healthy age- and sex-matched controls ($p < 0.0001$). In a recent meta-analysis (7), patients with rheumatoid arthritis had a three times higher risk of having thyroid autoantibodies than healthy controls [thyroglobulin autoantibody (TgAb): OR 3.17 (2.24–4.49) and thyroglobulin autoantibody (TPOAb): OR 2.33 (1.24–4.39)].

Although an association between thyroid autoimmunity and rheumatoid arthritis has been demonstrated, the causality is not yet established. However, there is increasing awareness of a possible common pathogenesis behind autoimmune diseases potentially caused by an underlying immunological breach resulting in disruption of self-tolerance (8). It is generally believed that both autoimmune thyroid disease and rheumatoid arthritis occur as a result of multiple factors (genetic susceptibility, endogenous, and environmental) (1, 9, 10). A malfunctioning T and B cell regulation causing reactions against autoantigens is involved in both conditions with antibody production in rheumatoid arthritis (rheumatoid factor and anti-cyclic citrullinated peptide) and thyroid autoimmunity (thyroid peroxidase, thyroglobulin, and thyroid stimulating hormone receptor antibodies) (1). Such T and B cell regulation is highly complex, but is intertwined with expression of various cytokines. Both cytokine production and B cell function are among the targets of newer biological antirheumatic agents (BAAs), which are increasingly used in the treatment of rheumatoid arthritis (11, 12). Current guidelines generally recommend treatment with BAAs when there is either insufficient response to treatment with the conventional disease modifying antirheumatic drugs or in the presence of unfavorable prognostic markers (autoantibodies, high disease activity, early erosions, and failure of two conventional disease modifying antirheumatic drugs) (11, 12). Although an increasing amount of antirheumatic agents exist, the most commonly used in the treatment of rheumatoid arthritis is the group of inhibitors of tumor necrosis factor-α (TNF-α). This pro-inflammatory cytokine plays a vital role in the immunological activation related to the autoimmune inflammatory patterns in rheumatoid arthritis. TNF-α expression has also been shown to be increased in patients with autoimmune thyroid disease, and therefore, treatment with TNF-α inhibitors could possibly effect thyroid autoimmune status as well (13). In previous studies of older immunomodulatory agents (e.g., interferon-α) in patients with multiple sclerosis and hepatitis C, it has long been known that thyroid autoimmunity develop in more than one-third of such patients (14–16). A mutual affection of the immune system in rheumatoid arthritis and thyroid autoimmunity makes the use of BAAs relevant also within the field of thyroid autoimmunity. The present review investigates the association between biological antirheumatic treatment of rheumatoid arthritis and affection of thyroid autoimmunity.

METHODS

In March 2017, a Medline literature search was performed using key terms of "rheumatoid arthritis," "thyroid," and alternately generic and commercial names of known BAAs. Identified studies were initially screened by title and abstract, and full text retrieved for further scrutiny. Further, the reference lists of included studies were checked. Only original studies evaluating thyroid autoimmunity during treatment with BAAs for rheumatoid arthritis were eligible for inclusion. Case reports were included and presented separately. All relevant data were carefully extracted from each included paper and txabulated independently by two authors (Sofie Bliddal and Stina Willemoes Borresen). Extracted data included: first author, publication year, number of patients, the studied BAA, patients' other medication, follow-up, method and cut-off used for detecting thyroid antibodies, known autoimmune thyroid disease, and thyroid status including autoimmunity before and after treatment with the BAA. Any disagreements were resolved by consensus. In some studies, the proportion of patients with positive thyroid antibodies was not reported directly, but could be calculated from study data.

RESULTS

Study Characteristics

A total of 14 relevant articles were identified. Upon scrutiny, five articles failed to comply with the inclusion criteria or had insufficient outcome reports of thyroid status, leaving six included articles (17–22), in a total 311 patients, and three were case reports (23–25). The studies included five prospective cohort studies of previous BAA-naïve patients with rheumatoid arthritis (17–20, 22) and one cross-sectional study of patients with rheumatoid arthritis who had received treatment with BAAs (**Table 1**) (21). The TNF-α inhibitors adalimumab (ADM), infliximab (INX), and etanercept (ETC) were used in three (17, 21, 22), four (18–21), and two (18, 21) studies, respectively. The monoclonal CD20 antibody rituximab (RIX) was used in two studies (20, 21). One of these was a cross-sectional study (21) and the other did not stratify results from patients treated with RIX from results of patients treated with the TNF-α inhibitor INX (20). One study (20) excluded patients with previously known thyroid disease, three studies (17, 21, 22) and two studies (18, 19) did not report whether they excluded these patients. All six studies reported the number of TPOAb-positive patients, and three studies (17, 20, 21) reported TgAb positivity. Additionally, two studies (20, 22) reported the TPOAb levels and one study (20) reported the TgAb levels. Two studies (20, 22) reported mean TSH and free thyroxine (FT4) levels.

Thyroid Autoimmunity

Biological antirheumatic treatment did not seem to affect the number of TPOAb-positive patients, which varied from 0 to 30% of patients at baseline and 0 to 25% at follow-up (**Figure 1A**; **Table 1**). Two studies reported a single patient turning TPOAb-positive after treatment with ADM (17, 22), and the number of TPOAb-positive patients was unchanged in two studies of INX (19) or INX/RIX (20), respectively. Likewise, only one TgAb-positive patient turned antibody-negative and none in a study of ADM (17) (**Figure 1B**). In the study of Caramaschi et al. (18), six patients treated with INX shifted from negative to positive thyroid antibodies and four patients shifted from positive to negative

TABLE 1 | Studies of thyroid status in rheumatoid arthritis patients treated with BAAs.

Reference	Study group	BAA	Dosage	Other treatment	Antibody assay	Antibody cut-off	Baseline		Follow-up time	Outcome	
							Antibody positivity	Thyroid function		Antibody positivity	Thyroid function
Atzeni et al. (17)	20 RA pts (17 women)	ADM	40 mg/2 weeks	MTX: 20/20 (100%) GC: 13/20 (65%) NSAID: 14/20 (70%)	ICMA (immulite 2000, DPC)	TPOAb: 35 IU/mL TgAb: 40 IU/mL	TPOAb: 6/20 (30%) TgAb: 8/20 (40%)	HT: 3/20 (15%)	6 months	TPOAb: 5/20 (25%) TgAb: 8/20 (40%)	NA
Caramaschi et al. (18)	54 RA pts (46 women)	INX $n = 43$ ETC $n = 11$	INX 3 mg/kg on week 0, 2, 6 and every 8 weeks ETC 2 × 25 mg/week	MTX: 52/54 (96%) Azathioprine: 2/54 (4%)	ELISA	TPOAb: 35 IU/mL TgAb: 40 IU/mL	TPOAb: 6/54 (11%) TgAb: 7/54 (13%) +4 Ab positive pts[a]	NA	12 months	TPOAb: 6/54 (11%), TgAb: 7/54 (13%) (12 INX, 1 ETC) Shift Ab-neg to Ab-pos: 6 pts Shift Ab-pos to Ab-neg: 4 pts (INX)[a]	All euthyroid
Elkayam et al. (19)	26 RA pts (17 women)	INX	3 mg/kg on week 0, 2, 6, and every 8 weeks	MTX 26/26 (100%)	ELISA (Zeus Scientific)	TPOAb: 25 IU/mL	TPOAb: 0/26	NA	14 weeks	TPOAb: 0/26	NA
Kaklamanos et al. (20)	36 rheumatic pts[b] (28 women)	INX $n = 18$ (14 RA pts) RIX $n = 18$ (12 RA pts)	INX 200, 350, or 500 mg RIX 2 × 1,000 mg/2 weeks or 4 × 500 mg/week	MTX: 13/36 (36%) Prednisolone: 16/36 (44%) Leflunomide: 3/36 (8%) HCQ: 2/36 (6%)	CMIA (Architect i2000, Abbott)	TPOAb: 5.61 IU/mL TgAb: 4.11 IU/mL	TPOAb: 4/36 (11%) TgAb: 6/36 (17%)\ TPOAb level (mean ± SD): 36.8 ± 44.9 TgAb level (mean ± SD): 10.6 ± 7.1	TSH (mean ± SD): 1.7 ± 1.2 mU/L FT4 (mean ± SD): 15.3 ± 3.7 pmol/L	3 years	TPOAb: 4/36 (11%) TgAb: 5/36 (14%) TPOAb level (mean ± SD): 20.2 ± 16.7 TgAb level (mean ± SD): 9.3 ± 5.5	TSH (mean ± SD): 1.8 ± 1.2 mU/L FT4 (mean ± SD): 15.4 ± 3.6 pmol/L
Koszarny et al. (21)	37 RA pts with a history of BAA treatment[c]	INX, ETC, ADM, or RIX[d]	NA	MTX, other DMARDs, prednisolone[d]	ELISA (Euroimmun)	TPOAb: 50 IU/mL TgAb: 100 IU/mL TRAb: 2 IU/mL	NA	NA	NA (cross-sectional)	TPOAb: 4/37 (11%) TgAb: 2/37 (5%)	NA
Raterman et al. (22)	138 RA pts with known thyroid status (106 women)	ADM	NA	MTX 108/138 (78%) Prednisolone 47/138 (34%) No. DMARDs used: 2–6	ELISA (Cobas® analyzer)	TPOAb: 34 IU/mL	TPOAb: 21/138 (15%) TPOAb level (median): 267 IU/mL	Mean TSH: 1.5 mU/L	6 months	TPOAb: 20/138 (15%) TPOAb level 201 IU/mL*	Mean TSH: 1.3 mU/L*

(*Continued*)

TABLE 1 | Continued

Reference	Study group	BAA	Dosage	Other treatment	Antibody assay	Antibody cut-off	Baseline		Follow-up time	Outcome	
							Antibody positivity	Thyroid function		Antibody positivity	Thyroid function
	Hypothyroid pts						TPOAb: 11/18 (61%)	18/138 (13%)	6 months	TPOAb: 12/18 (67%)	16/138 (12%)
							TPOAb level (median): 325 IU/mL	Mean TSH: 4.1 mU/L		TPOAb level (median) 282 IU/mL	Mean TSH: 3.5 mU/L
	Euthyroid pts						TPOAb: 9/113 (8%)	113/138 (82%)	6 months	TPOAb: 7/113 (6%)	7/138 (5%)
							TPOAb level (median): 114 IU/mL	Mean TSH: 1.4 mU/L		TPOAb level (median) 108 IU/mL	Mean TSH: 1.3 mU/L
	Hyperthyroid pts						TPOAb: 1/7 (14%)	7/138 (5%)	6 months	TPOAb: 1/7 (14%)	7/138 (5%)
							TPOAb level: 73 IU/mL	Mean TSH: 0.5 mU/L		TPOAb level 49 IU/mL	Mean TSH: 0.5 mU/L

[a]*Not reported whether TPOAb and/or TgAb.*

[b]*Twenty-six patients with RA, six patients with SLE, four patients with sero-negative arthritis. The study further included three different control groups.*

[c]*The number of female patients not reported. The study also included 38 patients BAA-naïve RA patients.*

[d]*The number of patients treated with each drug not reported.*

**p < 0.05 compared to baseline data.*

ADM, adalimumab; BAAs, biological antirheumatic agents; CMIA, Chemiluminescent microparticle immunoassay; ETC, etanercept; HCQ, Hydroxychloroquine; FT4, free thyroxine; HT, Hashimoto's thyroiditis; ICMA, immunochemiluminescence assay; INX, infliximab; MTX, methotrexate; NA, data not available; pts, patients; RA, rheumatoid arthritis; RIX, rituximab; TgAbs, thyroglobulin autoantibodies; TPOAbs, thyroid peroxidase autoantibodies; TRAbs, thyrotropin receptor autoantibodies.

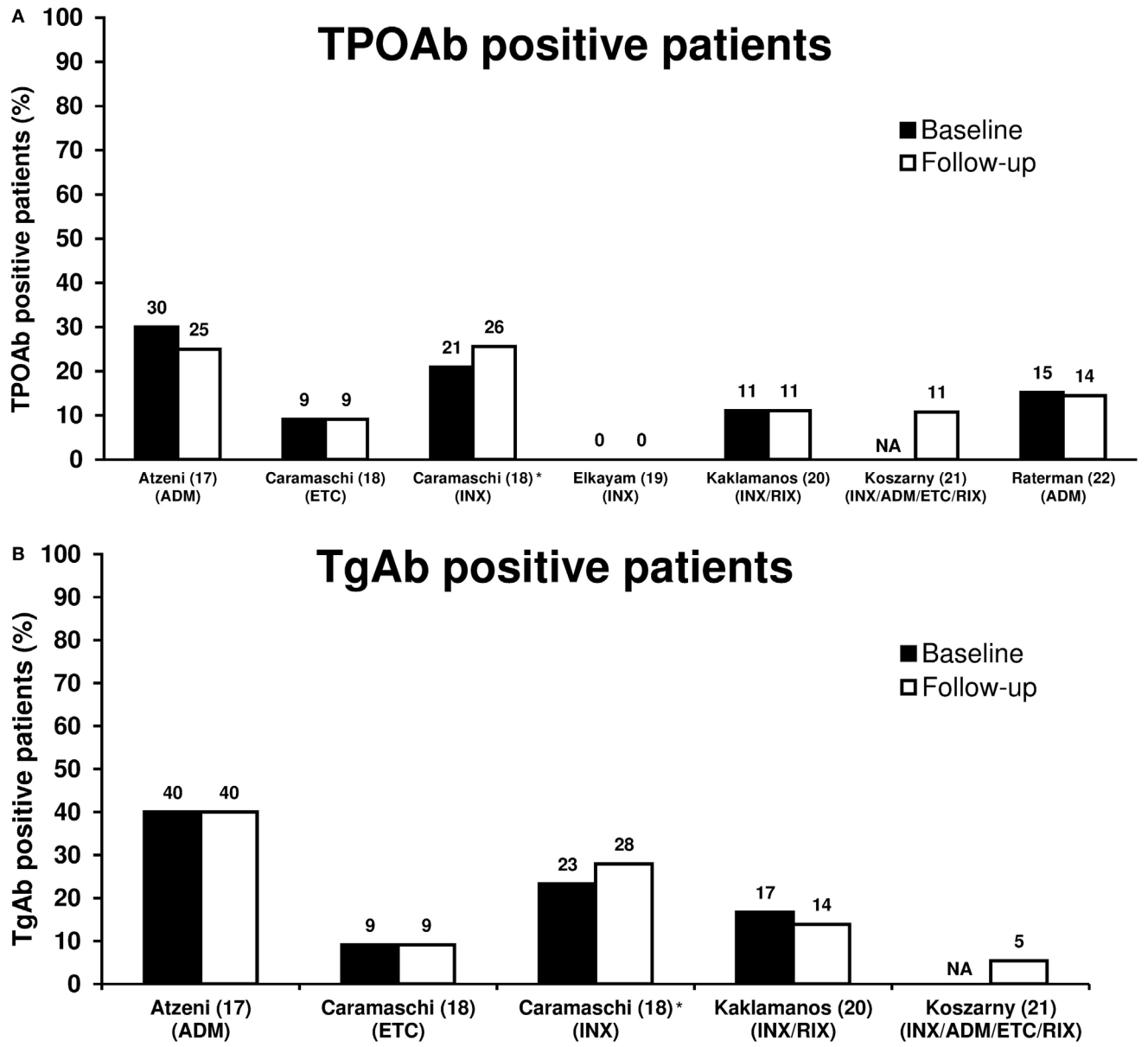

FIGURE 1 | Proportion of TPOAb-positive **(A)** and TgAb-positive **(B)** patients at baseline and follow-up in patients with rheumatoid arthritis treated with biological antirheumatic agents (BAAs). Studies are presented by first author name (reference number) (BAA). *In four patients at baseline and six patients at follow-up, no distinction was made between TPOAb-positivity and TgAb-positivity, and thus the reported thyroid autoantibody prevalence was included in both Figures 1A,B. Abbreviations: ADM, adalimumab; ETC, etanercept; INX, infliximab; RIX, rituximab; NA, not available. TgAb, thyroglobulin autoantibody; TPOAb, thyroid peroxidase autoantibody.

antibodies (no distinction was made between TPOAb and TgAb positivity). In a cross-sectional study (21), TPOAb-positivity was found in 4/37 (11%) patients with a history of biological antirheumatic treatment, which was similar to the 3/38 (8%) of patients who were BAA-naïve. The corresponding numbers of TgAb-positive patients were 2/37 (5%) and 4/38 (11%) for patients who had or had not received biological antirheumatic treatment, respectively.

Decreased or unchanged thyroid antibody levels were reported in two studies. In Raterman et al. (22), the mean TPOAb concentration decreased from 267 to 201 IU/mL ($p = 0.048$) in TPOAb-positive patients after 6 months of treatment with ADM. In Kaklamanos et al. (20), mean TPOAb concentration decreased insignificantly from 36.8 to 20.2 IU/mL in TPOAb-positive patients after 24–40 months treatment with INX or RIX. Likewise, mean TgAb concentration was unaffected in TgAb-positive patients (mean TgAb level 10.6–9.3 IU/mL) (20).

Thyroid Function

Two studies investigated changes in thyroid function before and after biological antirheumatic treatment (20, 22). In Raterman et al. (22), treatment with ADM led to a decrease in mean TSH

level from 1.5 to 1.3 mU/L ($p = 0.0014$) in the total group, whereas FT4 levels did not change. The decrease in TSH was larger in (previous) hypothyroid patients compared with euthyroid patients, but TSH also decreased in 8/10 of the hypothyroid patients who were not treated with L-thyroxine. Two of these patients became euthyroid after 6 months treatment with ADM (22). In Kaklamanos et al. (20), mean TSH changed from 1.7 to 1.8 IU/L, and FT4 changed from 15.3 to 15.4 pmol/L, yet both not significantly.

Cases

Our search revealed three case reports of autoimmune thyroiditis in patients with rheumatoid arthritis treated with a BAA. Two cases (23, 24) reported hyperthyroidism in patients treated with anti-TNFα. The first case (23) reported transient hyperthyroidism, lasting 1 month, in a patient after 6 months of treatment with ETC (TPOAb and TgAb negative, TRAb not measured). In a second case report (24), a 70-year-old women developed Graves' disease after 8 years of treatment with ADM. Interestingly, one case reported improvement of previously known autoimmune hypothyroidism in a patient after treatment with RIX (25). TPOAbs declined to undetectable levels after 6 months of treatment with RIX, and in an unchanged L-thyroxine dose the patient became clinically hyperthyroid with a TSH decline from 1.18 to 0.10 mU/L (25).

DISCUSSION

The present review showed that the BAAs used to treat rheumatoid arthritis did not seem to induce or worsen autoimmune thyroid disease. On the contrary, there was a tendency toward a positive effect; a reduction of TPOAb and TgAb concentrations and a reduction of TSH levels in hypothyroid patients. Despite the small number of included studies with diverse immunomodulatory agents (mainly TNF-α inhibitors, a few of RIX), the studies presented compliant data.

Due to its multiple immunological mechanisms, TNF-α has been previously investigated in thyroid patients. Both hypo- and hyperthyroid patients had significantly higher levels of TNF-α compared to controls, and in hyperthyroid patients successful treatment led to normalization of TNF-α levels (13). However, as demonstrated in the cases reported by van Lieshout (24) and Allanore (23), hyperthyroidism was diagnosed after initiation of anti-TNF-α therapy. It is difficult to assess whether this could be attributed to the treatment or an incidental finding due to a general susceptibility toward autoimmune thyroid disease in patients with rheumatoid arthritis (8). Also, autoimmune thyroid disease has been previously reported to fluctuate between hypo- and hyperthyroidism according to the prevailing subtype of (stimulating or blocking) thyrotropin receptor antibodies (26). These were not measured in the studies included in this review. Based on the results in the present review, alterations in thyroid autoimmune status upon anti-TNF-α treatment seem to be a minor concern and may very well be overshadowed by the potential benefit of such treatment—both in regard to the rheumatoid disease and possibly the thyroid autoimmune status.

Use of RIX, a monoclonal CD20 antibody causing B-cell-depletion, did not lead to significant changes in thyroid status or autoimmunity (TPOAbs/TgAbs) in the study by Kaklamanos et al. (20). In the case by Raterman et al. (25), treatment with RIX for rheumatoid arthritis may have affected the coexisting autoimmune hypothyroidism causing a shift to a (iatrogenic) hyperthyroid state after a few months of treatment with RIX and unchanged L-thyroxine dose. However, thyrotropin receptor antibody levels were not reported in the studies and no distinction was made between thyroid disease entities (Hashimoto's vs. Graves' disease). In Graves' disease complicated by moderate/severe orbitopathy, treatment with RIX has shown promising results (27, 28).

Unlike the known thyroidal side effects of immunomodulatory agents used in hepatitis C and cancer treatment, the immunomodulatory agents (anti-TNF-α and RIX) used in treatment of rheumatoid arthritis did not lead to significant changes in thyroid function nor autoimmunity. However, the well-established association between rheumatic diseases and thyroid autoimmunity necessitates continued monitoring of thyroid function in patients with rheumatoid arthritis and *vice versa* (5, 8, 29). Finally, it is advised to scrutinize each new immunomodulatory agent for its effect on thyroid as well as other autoimmune diseases and for each disease to be treated, in order to establish concise recommendations for follow-up of each agent and each disease (30).

AUTHOR CONTRIBUTIONS

SB and SWB are shared first authors and equally made primary contributions to data collection and analysis, interpretation of results, and writing of the manuscript. All authors contributed substantially to the study conception and design, interpretation of results, critical and intellectual revision of the manuscript, and all approved the final manuscript for publication.

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CASE REPORT
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The Daily Consumption of Cola Can Determine Hypocalcemia: A Case Report of Postsurgical Hypoparathyroidism-Related Hypocalcemia Refractory to Supplemental Therapy with High Doses of Oral Calcium

*Valentina Guarnotta[1†], Serena Riela[2†], Marina Massaro[2], Sebastiano Bonventre[3], Angela Inviati[3], Alessandro Ciresi[1], Giuseppe Pizzolanti[1], Salvatore Benvenga[4] and Carla Giordano[1]**

[1] Biomedical Department of Internal and Specialist Medicine (DIBIMIS), Section of Endocrine-Metabolic Diseases, University of Palermo, Palermo, Italy, [2] Department of Science and Technologies Biological Chemical and Pharmaceutical (STEBICEF), Section of Chemistry, University of Palermo, Palermo, Italy, [3] Department of General, Emergency and Transplant Surgery, Unit of General and Emergency Surgery, P. Giaccone Policlinico, Palermo, Italy, [4] Department of Clinical and Experimental Medicine, Endocrinology, University of Messina, Messina, Italy

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Edited by:
Bernadette Biondi,
University of Naples Federico II,
Italy

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Sapienza University of Rome,
Italy
Giampaolo Papi,
Ausl Modena, Italy

***Correspondence:**
Carla Giordano
carla.giordano@unipa.it

[†]These authors have contributed equally to this work.

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The consumption of soft drinks is a crucial factor in determining persistent hypocalcemia. The aim of the study is to evaluate the biochemical mechanisms inducing hypocalcemia in a female patient with usual high consumption of cola drink and persistent hypocalcemia, who failed to respond to high doses of calcium and calcitriol supplementation. At baseline and after pentagastrin injection, gastric secretion (Gs) and duodenal secretion (Ds) samples were collected and calcium and total phosphorus (P_{tot}) concentrations were evaluated. At the same time, blood calcium, P_{tot}, sodium, potassium, chloride, magnesium concentrations, and vitamin D were sampled. After intake of cola (1 L) over 180 min, Gs and Ds and blood were collected and characterized in order to analyze the amount of calcium and P_{tot} or sodium, potassium, magnesium, and chloride ions, respectively. A strong pH decrease was observed after cola intake with an increase in phosphorus concentration. Consequently, a decrease in calcium concentration in Gs and Ds was observed. A decrease in calcium concentration was also observed in blood. In conclusion, we confirm that in patients with postsurgical hypoparathyroidism, the intake of large amounts of cola containing high amounts of phosphoric acid reduces calcium absorption efficiency despite the high doses of calcium therapy.

Keywords: hypocalcemia, cola, hypoparathyroidism, hyperphosphatemia, calcium absorption

INTRODUCTION

The consumption of soft drinks, full of phosphoric acid, is a potential factor determining hypocalcemia, notably in patients with hypoparathyroidism. Postoperative hypoparathyroidism and subsequent hypocalcemia are the most frequent complications of total thyroidectomy. Generally, postoperative hypoparathyroidism is associated with transient hypocalcemia. Indeed about

60–70% of cases of postoperative hypocalcemia resolve within 4–6 weeks after surgery, while about 2–10% of patients develop chronic hypoparathyroidism and hypocalcemia (1). Only a small proportion of thyroidectomized patients receiving supplemental calcium therapy remains hypocalcemic (2, 3). Some patients' treatment fails to respond to calcium supplementation because of unrecognized celiac disease or, less frequently, through unknown causes.

In both the clinical (4, 5) and experimental settings (6), heavy consumption of cola soft drinks is associated with hypocalcemia, and with increased risk of bone fractures (7–9). Indeed, it is well known that in patients with normally functioning parathyroids, oral or parenteral phosphate intake can decrease serum calcium levels by reducing calcium intestinal absorption or increasing calcium excretion (10).

Therefore, patients with postoperative hypoparathyroidism may appear to be more fragile than other patients, if exposed to high doses of cola.

Here, we describe the case of a patient with postsurgical hypoparathyroidism-related hypocalcemia who was treated with high doses of oral calcium and calcitriol supplements, without reaching a good control of calcium levels.

BACKGROUND

A 28-year-old woman was hospitalized in our Section of Endocrinology with severe and recurrent hypocalcemic crises (12 times/year). She had undergone total thyroidectomy 8 months before our observation, with postsurgical hypoparathyroidism. She was treated with oral calcium carbonate (10 g/day), calcitriol (2 μg/day), and levo-thyroxine (125 μg/day). Serum total calcemia and phosphoremia were 6 and 5 mg/dL, respectively. Renal, hepatic functions, and serum electrophoretogram were normal. Urinary calcium and phosphorus ions were increased, while calcitonin levels were detectable, due to the persistence of a minimal micro thyroid tissue of 5 mm (**Table 1**). Celiac disease was excluded based on negativity for serum antibodies (anti-tissue transglutaminase and anti-endomysial), small bowel biopsy, and genetic testing (human leukocyte antigen test). Attempts to normalize calcemia with other calcium formulations (calcium carbonate plus gluconate, calcium lactate, and calcium citrate) were unsuccessful.

Careful evaluation of the patient's history revealed satisfactory compliance with the medical treatment but also habitual heavy daily cola consumption (about 2 L/day). We attempted a complete withdrawal of cola for 2 weeks, and the patient restored normal concentrations of both calcium and phosphorus ions in serum and urine (**Table 1**). Accordingly, the daily dose of calcium carbonate and calcitriol was decreased from 10 to 5 g/day and from 2 to 1 μg/day, respectively.

To understand the reasons for this significant decrease in calcium supplementation treatment, we designed a protocol evaluating the effect of oral diet cola intake on calcium absorption in the stomach and duodenum. This study was carried out in accordance with the recommendations of the University of Palermo/Policlinico Paolo Giaccone committee with written informed consent from the subject. Patient gave written informed consent in accordance with the Declaration of Helsinki and the recommendations of the University of Palermo/Policlinico Paolo Giaccone committee.

TABLE 1 | Baseline clinical and biochemical parameters at first observation and after the interruption of cola's intake.

Parameters	Baseline	After cola's interruption
Weight (kg)	66	67
BMI (kg/m^2)	25.2	25.6
Urea (mg/dL)	24	34
Creatinine (mg/dL)	0.9	0.8
Na^+ (mEq/L)	138	140
K^+ (mEq/L)	3.9	4.7
Cl^+ (mEq/L)	98	105
Ca^{2+} (mg/dL)	7	9.4
P (mg/dL)	6.5	4.7
Mg^{2+} (mg/dL)	1.6	1.7
Albumin (g/dL)	4.1	4.2
Total proteins (g/dL)	7.2	7.4
25 hydroxy vitamin D (ng/mL)	9.7	15.6
Parathyroid hormone (pg/mL)	1	1
Alkaline phosphatase (U/L)	16	19.6
Osteocalcin (ng/mL)	15	12
Glycemia (mg/dL)	84	78
Urinary calcium/24 h (g/day)	45	30
Urinary phosphorus/24 h (g/day)	70	29
AST (U/L)	15	14
ALT (U/L)	16	18
Beta C-terminal telopeptide (ng/mL)	0.2	0.2
TSH (μU/mL)	2.1	1.8
FT4 (ng/dL)	0.9	1
FT3 (pg/mL)	3.5	3.9
Calcitonin (pg/mL)	1.9	1.6

After an overnight fast, multilumen manometric probes in combination with an open-end tip were endoscopically placed *via* the nasal passage to take gastric secretion (Gs) and duodenal secretion (Ds). The baseline Gs pH was 2.6.

An hour before the experimental procedure, a single dose of calcium carbonate (2 g) was administered orally to the patient. At baseline, 10 mL of Gs and Ds samples were obtained, and calcium and total phosphorus ($P_{tot} = H_3PO_4$, $H_2PO_4^-$, HPO_4^{2-}, and PO_4^{3-}) concentrations were evaluated. In addition, the calcium, P_{tot}, sodium, potassium, magnesium, chloride, and vitamin D concentrations in the blood were evaluated.

Pentagastrin (6 μg/kg) was injected to stimulate Gs. After 5 and 30 min, Gs and blood samples were collected and the concentrations of calcium, P_{tot}, sodium, potassium, magnesium, and chloride ions were estimated.

Afterward, the patient orally took 1 L of diet cola, without sugar, to avoid the simulation of endogenous insulin secretion and intracellular phosphate shift, over 180 min (330 mL every 60 min). Gs was drawn from the stomach every 15 min over 180 min after administration of cola, whereas Ds was collected at times 60, 75, 120, and 180 min. In addition, blood samples were obtained every 30 min over 180 min (**Figure 1**). At the end of the procedure, a urine sample was collected for determination of the urinary calcium and phosphorus.

The day after, pH monitoring was done by placing a pH probe (5 cm) above the upper border of the manometrically determined lower esophageal sphincter.

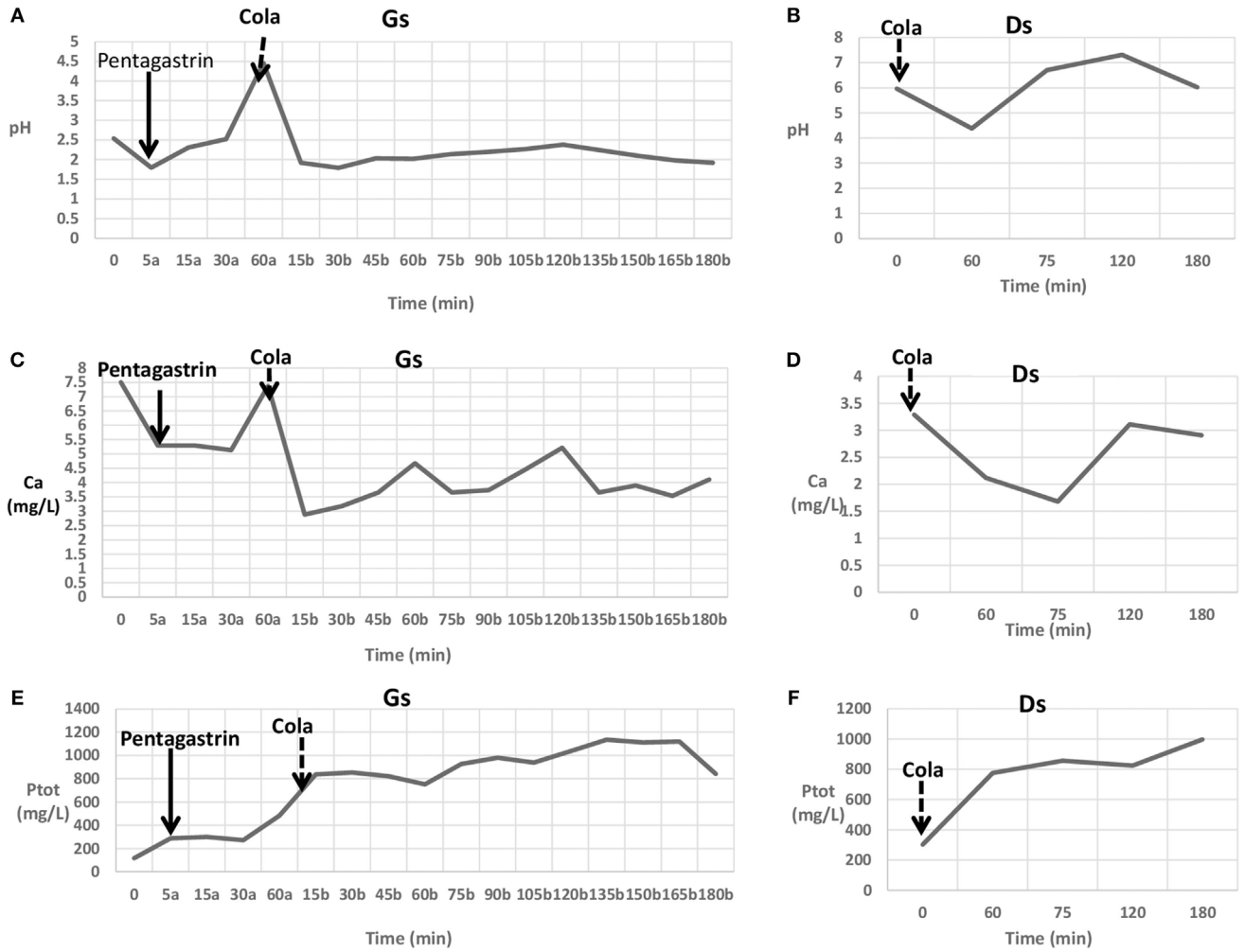

FIGURE 1 | **Gastric secretion (Gs) analysis during pentagastrin stimulation (a) and cola intake (b)**. **(A)** pH changes in gastric content. **(C)** Ca changes in gastric content. **(E)** Total phosphorus (P_{tot}) changes in gastric content. Duodenal secretion (Ds) changes before (time 0) and after cola intake. **(B)** pH changes in duodenal content. **(D)** Ca changes in duodenal content. **(F)** P_{tot} changes in duodenal content.

In basal conditions, serum calcium, phosphorus, magnesium, sodium, potassium, chloride, glycemia, and urinary calcium and phosphorus were in the normal range (results not shown), as were the gastric and duodenal P_{tot} levels (**Figure 1**). A pentagastrin injection caused a slight decrease in pH after 5 min followed by an increase over 60 min (**Figure 1**). No differences were observed for serum and urinary parameters (results not shown). A slight change in gastric calcium and phosphorus was observed from 5 to 30 min after a pentagastrin injection, whereas a remarkable increase in P_{tot} level was observed after 60 min (**Figure 1**).

Cola drinking caused a strong decrease in pH value (**Figure 1**), and both in stomach and in duodenum, a strong reduction of calcium concentration and a concomitant increase of phosphorus concentration (**Figure 1**) were detected.

A similar trend was observed in serum, namely a decrease in calcium concentration (9.4 vs. 8.0 mg/dL) and an increase in the phosphorus one (3.8 vs. 5.6 mg/dL). In addition, increases in the calcium/creatinine ratio (29.2 vs. 48.4) and phosphorus/creatinine ratio (67.8 vs. 109.8) were observed. No differences in sodium, potassium, chloride, magnesium, and glycemia levels were detected (results not shown).

Slight but not significant gastroduodenal reflux was detected by the pH meter.

DISCUSSION

This report describes a case of a patient with severe hypocalcemia secondary to iatrogenic hypoparathyroidism, who because of cola consumption was not responsive to high doses of oral calcium and calcitriol supplementation.

As is well known, calcium is generally absorbed by two general mechanisms in the small intestine. The transcellular active process, located in the duodenum and upper jejunum, involves three major steps: calcium entry across the brush border by calcium transport protein (CaT1); intracellular diffusion, mediated largely by calbindin; and extrusion, mediated

by calcium pumps ATPase dependent calcium pumps. The paracellular, passive mechanism occurs in the entire intestine. When calcium intake is low, transcellular calcium transport accounts for a large fraction of the absorbed calcium. When calcium intake is high, transcellular transport accounts for a small part of the absorbed calcium, because CaT1 and calbindin are downregulated (11).

It has been reported that the precipitation of calcium phosphate salts is initiated by a reaction of the calcium and hydrogen phosphate ions, leading to calcium hydrogen phosphate (12–14). The maximal product of the molar concentrations of these ions, which can exist in solution without precipitation, defines their solubility product. When this solubility product exceeds the normal value, precipitation occurs. The solubility product for calcium hydrogen phosphate has been estimated *in vitro* under physiological conditions of temperature, ionic strength, pH, and comparable Ca/P molar concentration ratios (11, 12), and the estimates range from 2.4 to 2.5×10^{-6} mol/L.

As is well known, cola represents a strong exogenous source of phosphate, due to high phosphorus content (about 15–20 mg/dL), more than other carbonated soft drinks (15). In this case, the consumption of cola (330 mL every 60 min) caused a sudden change in the pH gastric values as a consequence of the strong cola acidity (pH 1.8). The effect of cola on the calcium concentration seems to be connected to its high phosphate concentration. Indeed, when the cola drink was ingested a considerable decrease in the calcium concentration and, of course, an increase in the phosphorus concentration was observed. After this effect, due to the formation of calcium phosphate species, an increase in both calcium and phosphorus concentrations was detected, probably due to slow release (dissociation) of calcium and phosphorus species. The intake of a second (after 60 min) and third (after 120 min) cola drink caused a qualitatively comparable effect on the calcium and phosphorus ions. Notably, only a small concentration of Ca^{2+} ions is available during the consumption of cola. These effects were observed both in stomach and in duodenum. Indeed, the intestinal content variations largely reflect those of the stomach.

Unexpectedly, a small pH variation was observed during the experimental procedure. Indeed, after the first significant change from 2.54 up to 1.92, the pH value seems to fluctuate around 2.2 ± 0.2.

A comparison between the gastric calcium and phosphorus levels after pentagastrin stimulation and cola intake might suggest that cola has the effect of slowing down the reset of the initial calcium concentration and increasing phosphorus levels, more than pentagastrin (**Figure 1**). Consequently, the low intestinal calcium absorption caused a sudden decrease in serum calcium levels and an increase in phosphorus serum levels. As expected, the absence of parathyroid glands caused a sharp increase in tubular phosphate reabsorption during cola intake.

Our data show that phosphorus ions lower serum calcium levels by a simple physicochemical precipitation of calcium hydrogen phosphate as its solubility product exceeds the normal value.

Other previous reports described a significant effect of cola on bone (9). Indeed, diets full of phosphorus and low in calcium lead to complexes that reduce serum calcium, stimulating PTH, which, in turn, causes bone resorption. High dietary phosphorus has been demonstrated to cause bone loss in animals (16). In addition, in another study, cola was given to ovariectomized rats with subsequent hypocalcemia and loss of bone mineral density. However, a limit of the current study is not to have evaluated the direct effect of caffeine on hypocalcemia, using a decaffeinated cola. Both caffeine and coffee can stimulate gastric acid secretion and decaffeinated coffee raises serum gastrin levels (17–19), even though the amount of caffeine in cola is not very high.

These findings suggest that in patients with postsurgical hypoparathyroidism, the intake of large amounts of phosphoric acid may reduce calcium absorption efficiency despite the high doses of calcium therapy, because the deficient PTH cannot balance hyperphosphatemia. However, further research is required in order to confirm the results observed.

CONCLUDING REMARKS

The evidence of severe hypocalcemia in patients with hypoparathyroidism requires evaluation of the causal factors. In patients taking high doses of calcium without benefits, the intake of cola drinks should always be considered, and when hypoparathyroidism is also present, a low phosphorus diet is advisable.

AUTHOR CONTRIBUTIONS

VG, AC, GP, SB, and CG analyzed and interpreted the patient data regarding the clinical and hematological aspects. SR and MM analyzed the chemical data from Gs and Ds samples. SB and AI performed the experimental procedure introducing the probes in the stomach and duodenum. VG, SR, and SB contributed in writing the manuscript. All the authors revised and approved the final manuscript and agreed to be accountable for the content of the work.

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MINI REVIEW
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Autoimmune Abnormalities of Postpartum Thyroid Diseases

Flavia Di Bari[1], Roberta Granese[2], Maria Le Donne[2], Roberto Vita[1] and Salvatore Benvenga[1,3,4]*

[1] Department of Clinical and Experimental Medicine, University of Messina, Messina, Italy, [2] Department of Obstetrics and Gynecology, University Hospital "G. Martino", Messina, Italy, [3] Master Program on Childhood, Adolescent and Women's Endocrine Health, University of Messina, Messina, Italy, [4] Interdepartmental Program of Molecular & Clinical Endocrinology, and Women's Endocrine Health, University Hospital "G. Martino", Messina, Italy

The year following parturition is a critical time for the *de novo* appearance or exacerbation of autoimmune diseases, including autoimmune thyroid disease. The vast majority of postpartum thyroid disease consists of postpartum thyroiditis (PPT) and the minority by Graves' disease and non-autoimmune thyroiditis. PPT has a worldwide prevalence ranging from 1 to 22% and averaging 5% based on a review published in 2012. Several factors confer risk for the development of PPT. Typically, the clinical course of PPT is characterized by three phases: thyrotoxic, hypothyroid, and euthyroid phase. Approximately half of PPT women will have permanent hypothyroidism. The best humoral marker for predictivity, already during the first trimester of gestation, is considered positivity for thyroperoxidase autoantibodies (TPOAb), though only one-third to half of such TPOAb-positive pregnant women will develop PPT. Nutraceuticals (such as selenium) or omega-3-fatty acid supplements seem to have a role in prevention of PPT. In a recent study on pregnant women with stable dietary habits, we found that the fish consumers had lower rates of positivity (and lower serum levels) of both TPOAb and thyroglobulin Ab compared to meat eaters. Finally, we remind the reader of other diseases that can be observed in the postpartum period, either autoimmune or non-autoimmune, thyroid or non-thyroid.

Keywords: postpartum thyroiditis, thyroid autoimmunity, non-autoimmune thyroiditis, Graves' disease, thyroid autoantibodies

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Eijun Nishihara, Kuma Hospital, Japan

****Correspondence:***
Flavia Di Bari
flaviadb1983@libero.it

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INTRODUCTION

The postpartum period, especially its first year, is a critical time for the onset, exacerbation, or relapse of autoimmune diseases. The literature on this topic is relatively scarce, as a PubMed search run on February, 2017 by using the string "postpartum and autoimmunity" yielded only 139 articles. Before discussing of postpartum thyroid diseases (PPTDs) and especially of postpartum thyroiditis (PPT), we would like to remind the existence of autoimmune endocrine diseases involving glands other than thyroid (1–20) as well as of thyroid diseases of non-autoimmune nature (21–27), as summarized in **Table 1**.

POSTPARTUM THYROID AUTOIMMUNITY

Postpartum Graves' Disease (GD)

As well known, GD is an autoimmune disorder characterized by hyperthyroidism, with or without associated ophthalmopathy. Its pathogenesis is related to loss of tolerance to autoantigen thyroid-stimulating hormone receptor that leads to the infiltration of the gland.

TABLE 1 | Endocrinopathies in the postpartum period.

Endocrinopathy	Comments
Postpartum Addison's disease (1–7)	It is a rare disease. Its diagnosis can be overlooked during pregnancy and after parturition. Indeed, fatigue, anorexia, vomiting, and hyperpigmentation can be easily confused with similar symptoms that occur frequently during gestation and/or postpartum. Because unrecognized, acute, and frequently fatal addisonian crises may occur in the postpartum period
Hypopituitarism [Postpartum lymphocytic hypophysitis (PPLH) and Sheehan's syndrome] (8–20)	PPHL or autoimmune hypophysitis is mostly observed in women during pregnancy or after delivery, though it may also occur in males and children. PPLH is frequently associated with autoimmune diseases, particularly with Hashimoto's thyroiditis
	Either PPLH or the non-autoimmune postpartum pituitary gland ischemic necrosis (Sheehan's syndrome) can be associated with postpartum thyroiditis (PPT)
Non-autoimmune thyroiditis (21–27)	This form of thyroiditis is far less frequent than PPT
	Infective forms of thyroiditis with subacute or acute course have been reported in the postpartum setting caused by *Brucella melitensis* or *Mycobacterium tuberculosis*. The symptoms reproduce a thyrotoxic picture (nervousness, palpitations, and loss of weight) with moderately painful goiter and fever (37.5°C). It is important to emphasize that in some cases inflammatory changes seen in subacute thyroiditis can obscure sonographic evidence of underlying papillary thyroid cancer. Also, a clinical picture of painful thyroid enlargement, even with fever, and local mechanical complications can be due to intrathyroid hemorrhages

Studies indicate that new-onset autoimmune thyroid disease (AITD) "occurs in up to 10% of all women in the postpartum period and that up to 60% of GD patients in the reproductive years give a history of postpartum onset" (28).

Two contemporary Canadian studies in the same province (Ontario) but in different areas and on different categories of women found different frequencies of PPT and postpartum GD (29, 30). The Toronto area study on 1,372 unselected women found that 78 (5.7%) had PPT and 3 (0.22%) GD; in addition, 1 other woman (0.07%) had postpartum thyrotoxicosis due to toxic nodular goiter (29). Thus, the PPT to postpartum GD ratio was 78:3 (26:1). Instead, in 40 Canadian women with type 1 diabetes mellitus (DM1) residing in the Hamilton area, the ratio was 9:1, since PPTD consisted of PPT in 9 patients (22.5%) and postpartum GD in 1 patient (2.5%) (30). The ratio between PPT and postpartum GD can be inferred from additional studies. In one Iranian investigation on 1,040 pregnant women (31), 119 had PPT (11.4%) and only 1 GD (1%), with a ratio of 119:1. Instead, a Spanish study on 641 pregnant women (32), not all of whom sampled at all-time points throughout 12 months postpartum, found that 45 developed PPT [incidence rate 7.8%; confidence interval (CI) 5.6–10%], 8 developed GD (incidence rate 1.5%; CI 0.5–2.5%) and 3 developed non-palpable toxic thyroid adenoma-associated hyperthyroidism (incidence rate 0.5%; CI 0–1.5%). Thus, the ratio between PPT and postpartum GD was 6:1. Incidentally, this 8:3 (2.7:1) ratio between postpartum GD and postpartum toxic adenoma matches the 3:1 ratio of the aforementioned Canadian study (29). According to Japanese authors (33), the frequency of postpartum GD in the general population is estimated at around 0.5%, that is, 1 in 200 postpartum women.

In two retrospective Italian studies (34, 35), the postpartum period was a risk factor for relapse(s) of GD, not for the onset. Instead, an earlier Swedish study concluded for a risky role of the postpartum period in the onset of GD (36). In this study (36), 93 consecutive women with GD aged 20–40 years were examined for a possible relation between onset of GD and previous pregnancy. An increased relative risk of developing GD within 1 year following delivery was found (RR = 6.5, CI 3.8–11.0). After excluding the nulliparous women, almost two out of three women who developed GD in the childbearing age of 20–35 years had a postpartum onset, suggesting an important role of immunomodulatory events following delivery for the development of this disease in young women. A similar relative risk (that is, RR = 5.6) was reported for American women aged 35–39 years (37). This is retrospective study on 152 consecutive women, aged 18–39 years when diagnosed with GD (37). The authors found that, in parous women, 45% were diagnosed with GD in the postpartum period and 55% had an onset in subsequent years. The risk of developing post-pregnancy GD was the greatest in the age band 35–39 years, with 56% of them developing GD compared to 42% of nulliparous women (37). In a Japanese retrospective study on 289 consecutive women with GD, 92 were of childbearing age (20–39 years) and had one or more deliveries (38). At least 37 patients had evident postpartum onset of the disease. Thus, at least 40% of GD women aged 20–39 years developed their disease during the postpartum period (38). In another study, in women diagnosed with GD during the ages of 20–35 years, 66% had a postpartum onset, and women with a previous history of GD relapsed frequently in the postpartum period (39).

In a French study (40), 98 patients with GD were compared to 95 patients with Hashimoto's thyroiditis (HT) and to 97 patients with benign thyroid nodules (control group) in order to evaluate the triggering role of pregnancy and other major stressors in the occurrence of AITDs. A stress factor was encountered in 11% of GD women and 6% of HT or thyroid nodularity women, an insignificant difference. Instead, in women of childbearing age, GD after a pregnancy occurred more frequently than HT or benign thyroid nodules (25 vs. 10 or 13%, $p < 0.05$). The author concluded that the role of stressors, if any, in triggering GD seems to be weak and dubious compared to the role of pregnancy and postpartum.

Concerning possible prevention of GD relapse in the postpartum, continuing antithyroid drugs therapy throughout pregnancy

prevents recurrence of GD without neonatal hypothyroidism or malformations (41). However, the use of methimazole is related to its potential teratogenic effects, especially in the first trimester of pregnancy (42).

Concerning medical therapy of GD and in view of the reference made to the omega-3 fatty acids-rich fish in the next heading, it is noteworthy mentioning the following case (43). A professor of physiology self-reported her GD developed 4 months postpartum with a TSH normalization, within 8 weeks of beginning flaxseed oil supplement (5–1,000 mg tablets twice a day). Flaxseed oil is over 50% omega-3 fatty acids (mainly alpha-linolenic acid), but it also contains about 15% omega-6 fatty acids (mainly linoleic acid) (43).

It is noteworthy that GD and PPT may affect the same woman, at different times. A clear case of PPT (in the form of transient thyrotoxicosis) in a young woman in whom GD had appeared 6 years earlier was reported (44). Shortly prior to becoming pregnant, an increase in thyroperoxidase autoantibodies (TPOAb) was observed in this woman. In another Japanese woman with thyroid hemiagenesis, GD was present in the pregnancy that preceded the postpartum period during which PPT appeared (45). Other case reports of PPT following GD have appeared in the literature (46, 47), one being noteworthy because of the sequence onset of GD → PPT → relapse of GD (47). The chronological sequence of PPT preceding GD was described in three young Caucasian women (48, 49). Based on the different pattern of radioiodine thyroid uptake, rate of positivity and mean levels of TSH-binding inhibiting antibodies, and evolution of hyperthyroidism in almost 100 women with GD followed up in the postpartum period, it was concluded that PPTD develops frequently in the postpartum period of patients with GD (50).

Finally, concurrent Sheehan's syndrome and GD in the postpartum has been reported (51). In this case report, GD appeared first and Sheehan's syndrome later.

Postpartum Thyroiditis

In this minireview, we will focus on the endocrine and autoimmune side of PPT, with no reference to the neuropsychological disturbances, particularly the association with postpartum depression (52, 53). Neuropsychological disturbances, such as acute psychosis, can also occur in association with postpartum GD (54). Very recently, we have reviewed the postpartum mood disorders (55).

Postpartum thyroiditis is a thyroid dysfunction, characterized by lymphocytic infiltration of the gland, which appears in the first postpartum year in women who were euthyroid prior to pregnancy (42, 53). The just released guidelines of the American Thyroid Association (42) endorse the original definition by Amino et al. (56), namely PPT is "the occurrence of thyroid dysfunction, excluding GD, in the first postpartum year in women who were euthyroid prior to pregnancy."

Epidemiology and Risk Factors

Based on a review published in 2012 (53), PPT has a worldwide prevalence of approximately 5%, but ranging from 1 to 22%. Because of its autoimmune nature, other autoimmune disorders may appear years after PPT. In one study, 40 women (mean age 36 years) with documented PPT 5 years earlier and 30 age-matched healthy women who all had undergone normal delivery an average of 5 years previously, were investigated (57). Women with previous PPT had symptoms of dry eyes, caries, arthralgias, swollen joints, and fatigue significantly more often than control group ($p < 0.05$). One-third (34%) of the women were anti-SSB positive and 46% were anti-SSA positive at follow-up. Furthermore, 15/35 women with a history of PPT had objectively reduced tear and/or saliva secretion; 5/24 investigated women had keratoconjunctivitis sicca, and 2/7 salivary gland biopsies showed chronic lymphocytic sialadenitis. Three women (8.6%) had both xerophthalmia and xerostomia. The authors concluded that features of Sjögren's syndrome are frequent in young women with previous PPT (57).

Several factors confer risk for the development of PPT, a major one being serum positivity for thyroid autoantibodies (TAb) during gestation (53). Furthermore, based on a systematic review (58), the risk for PPT conferred by positivity for TAb during gestation is much greater than the risk for other outcomes. Indeed, compared with women who are TAb negative, odds ratio (OR) for maternal PPT was 11.5, greater than the OR for miscarriage (3.73), recurrent miscarriage (2.3), preterm birth (1.9), or unexplained subfertility (1.5) (58). Paralleling GD, parturition can be a risk factor for autoimmune thyroiditis (AIT) (59). Women with at least one pregnancy had increased likelihood for AIT (OR 4.6, $p < 0.05$) compared to women who have never been pregnant. Similar results were observed using hypoechogenic thyroid pattern (OR 1.7, $p < 0.05$) and positive TPOAb levels (OR 1.8, $p = 0.05$) as separate dependent variables or using number of births as alternate independent variable. Furthermore, immune rebound after parturition may cause not only AITD, including PPT, but other autoimmune diseases: postpartum renal failure or postdelivery hemolytic–uremic syndrome, postpartum idiopathic polymyositis, postpartum syndrome with antiphospholipid antibodies, and postpartum autoimmune myocarditis (60).

Women with other autoimmune disorders as systemic lupus erythematosus (61), chronic viral hepatitis (62), DM1 (63–66), multiple sclerosis (67), and antipituitary antibodies positivity (19) have an increased risk of PPT (42) (**Table 2**). Other conditions that can predispose to develop PPT, such as gestational diabetes (68), are summarized in **Table 2**. Also, PPT may develop years after irradiation of the neck for lymphoma (69).

Considering the relative rarity of the thyroid hormone resistance (RTH) syndrome, a non-autoimmune genetic disorder in which elevated circulating levels of thyroid hormones fail to suppress serum TSH, it is worthwhile mentioning two cases of association between RTH and PPT (70, 71) (**Table 2**). This association has been reported also outside of the postpartum setting (72). Concerning the role of cigarette smoking as a risk factor for PPT, data are controversial (73–75) (**Table 2**).

Postpartum Thyroid Hormone Autoantibodies

Positivity for TPOAb, already during the first trimester of gestation, is the best humoral marker for predictivity of PPT; nonetheless, only 33–50% of these women will develop PPT, whereas TAb-negative women have a very low incidence of PPT (53).

TABLE 2 | Frequency of postpartum thyroiditis (PPT) in women with the indicated disease or condition.

Reference	Disease/condition	Population studied	Frequency of PPT	Comments
Stagnaro-Green et al. (61)	Systemic lupus erythematosus (SLE)	63 pregnant women with SLE	14%	
Elefsiniotis et al. (62)	Chronic viral hepatitis (HCV and HBV)	21 women with chronic HCV infection and 74 women with chronic HBV, of whom 16 and 64 finally included in the study	Four of 16 chronic HCV-infected women (25%) and none of 64 chronic HBV infected women developed PPT	All chronic HBV-infected women had never been treated before whereas 3 of 16 chronic HCV-infected women had been treated in the past with pegylated-interferon alpha plus ribavirin
Bech et al. (63)	Type 1 diabetes mellitus (DM1)	85 pregnant women with DM1	10.5%	
Gallas et al. (64)	DM1	126 pregnant women with DM1	15.9%	Patients with postpartum thyroid disease (PPTD) were slightly older than those without PPTD and the prevalence of TPO-Ab was higher in these women
Alvarez-Marfany et al. (65)	DM1	41 pregnant women with DM1	25%	25% was threefold greater in a non-diabetic population studied by the same group of authors. Forty-three percent of the women (3/7) who developed PPTD required treatment in the immediate postpartum period and at long-term follow-up (permanent hypothyroidism)
Gerstein (30)	DM1	51 pregnant women with DM1, 40 of whom completed follow-up	22%	Postpartum thyroid dysfunction occurred in 10 of 40 patients (25%; 95% confidence interval, 12.7–41.2%); PPT developed in 9 patients (22.5%) and postpartum Graves' disease developed in 1 patient (2.5%)
Triggiani et al. (66)	DM1	15 DM1 pregnant women vs 10 age-matched healthy controls	13.3% in DM1 women vs 20% in healthy controls	
Jalkanen et al. (67)	Multiple sclerosis (MS)	46 MS pregnant women vs 35 age-matched healthy controls	3.4% in MS women vs 2.9% in healthy controls	PPT rate in MS and controls was similar (3.4 and 2.9%) despite the fact that the rate of elevated serum levels for thyroid autoantibodies (TAb) at 6 months postpartum was sixfold greater in MS (35.3 vs 5.7%)
Komatsu et al. (69)	Irradiation of the neck	Case of a 30-year-old Japanese woman		Irradiation therapy to the neck for malignant lymphoma 9 years earlier
Paragliola et al. (70)	Thyroid hormone resistance (RTH) syndrome	Case of a 30-year-old Italian woman		RTH was due to a mutation of thyroid hormone receptor β, but occurring at different codons in these two women
Taniyama, et al. (71)		Case of a 44-year-old Japanese woman		
Galanti et al. (73)	Smoking cigarettes	874,507 parous women smoking during pregnancy	Thyroiditis within 6 months from childbirth was positively associated with smoking (adjusted HR = 1.88)	Smoking may increase the risk of thyroiditis occurring in the postpartum
Balázs and Farid (74)	Smoking cigarettes	22 pregnant women with previous PPT vs 21 pregnant women without thyroid disease	12/22 women with previous PPT had recurrent disease. Half of these women had high thyroglobulin Ab or thyroperoxidase autoantibodies in the first trimester compared to none among those without recurrent PPT and 2/21 controls	Women with recurrent PPT were more likely to be smokers
Stagnaro-Green et al. (75)	Smoking cigarettes	4,394 women screened for thyroid function and TAb at 6 and 12 months postpartum	3.9%	No increased risk for PPT by smoking was found

Some studies have reported the appearance of thyroid hormones autoantibodies (THAb) in postpartum period that can interfere with the evaluation of thyroid function. Jansson and Forberg described the presence of Ab against T3 in a woman who developed biphasic PPT, namely thyrotoxicosis followed by transient hypothyroidism after childbirth (76). In another study, three women with PPT had spuriously increased concentrations of free thyroid hormones because of antibody binding of radiolabeled T4 and T3 analogs. The antibody binding of radiolabeled analogs disappeared by 48 weeks postpartum. Postpartum women who develop THAb have about 2% prevalence of increased binding of radiolabeled analogs, which can

result in an interference in thyroid hormone assays (77). Thus, it was suggested that women with PPT should receive full thyroid-function testing and be checked for possible antibody binding of analog tracers if free thyroid hormone levels are inappropriately increased (77).

Recently, the first case of transient appearance of THAb in pregnancy was reported (78). A 35-year-old pregnant woman, with a known diagnosis of HT, and under levothyroxine (L-T4) replacement therapy, was clinically euthyroid with normal TSH but elevated free triiodothyronine (FT3) and free thyroxine (FT4). Serum FT4 and FT3 returned progressively normal postpartum. The presence of circulating THAb was confirmed by demonstrating THAb against the two hormones (78).

In a Welsh larger study, THAb were searched, from week 4 through week 48 postpartum, in 148 thyroid antibody-positive women and 261 thyroid antibody-negative women (77). The study started with selecting, in the 409 women, those showing interference in the FT4 and/or FT3 assays using the corresponding free thyroid hormone Amerlex assay (77). Only 3 of the 148 women thyroid antibody-positive women (2.0%) had THAb, particularly T3-analog Ab ($n = 1$), T3-analog and T4-analog Ab ($n = 2$). Only two of the three women had PPT. Previously, the same group (79) found that the rate of THAb, as estimated by the interference (overestimation) of FT4 and/or FT3 by the Amerlex analog method, was 0.04% (1/2460), 50-fold less than the above 2.0%.

In these three women (77), THAb measured by non-specific precipitation of serum enriched with radiolabeled Amerlex-T4 analog or Amerlex T3-analog immunoglobulin classes, could not be identified. In the same three women (77), antibody binding of radiolabeled analogs and its effect (overestimation) on free T4 and free T3 assays disappeared by 48 weeks postpartum. However, there is the extreme variability of the THAb in causing interference.

In brief, one cannot predict the presence of THAb based simply on the interference (overestimation) in the assay of free thyroid hormones, since this interference is frequently absent. Furthermore, the greater the frequency of sampling and associated THAb search over a given time course, the greater the chances to detect THAb. Until now, there is no study that has evaluated their role as predictors for future development of PPT. However, it is noteworthy that THAb (at least one among T3IgM, T3IgG, T4IgM, and T4IgG) are highly prevalent in patients with DM1 (80), an autoimmune endocrine disorder that confers high risk for PPT (**Table 2**).

Clinical Picture

The clinical course of PPT is similar to subacute thyroiditis but in absence of anterior neck pain or tenderness of the thyroid (53). The classic form is characterized by transient hyperthyroidism (8–24 weeks postpartum), followed by a phase of transient hypothyroidism (3–12 months postpartum), and then by return to euthyroidism at the end of the initial postpartum year. However, the clinical course of PPT is variable because about 25% of women presenting the classical form, 25% isolated thyrotoxicosis, and one-half presenting isolated hypothyroidism (53). In the thyrotoxic phase, asthenia and irritability are the most frequent symptoms; instead, lack of energy, aches and pains, poor memory, dry skin, paresthesias, and cold intolerance are the most frequent hypothyroid features (81).

Approximately half of PPT women will have permanent hypothyroidism (53). Unless evolved into permanent hypothyroidism, PPT tends to recur after subsequent deliveries. A Welsh study (82) reported a 70% chance of developing recurrent PPT after the first PPT attack, and a 25% risk even in women who were only TPOAb positive without thyroid dysfunction during the first postpartum period.

Diagnosis

The diagnostic procedures depend on the phases of the disease. In the thyrotoxic phase (TSH suppressed with increased serum FT3 and FT4), it may be necessary to differentiate PPT from GD. In GD, radioactive iodine uptake is high, while it is low in PPT, but this test is contraindicated during breastfeeding. Therefore, in these cases, the dosage of thyroid receptor antibodies is useful: in PPT, they are absent in almost all cases. Also, the thyroid echography can to show an increased hypoechogenicity in many cases of PPT. In the hypothyroid phase, TSH levels are increased with low or normal FT4 concentrations (81). However, during postpartum, the susceptible period to develop GD and PPT is different: around 3 months for PPT vs later than 6 months for GD (83).

Nutraceuticals, Food, and Prevention Strategy of PPT

Selenium, through selenoproteins, has a key action on thyroid function by protecting thyrocytes from oxidative damage (84). Moreover, selenium supplementation can ameliorate thyroid autoimmunity in patients with mild-form or early-stage HT (85). Also, when given to pregnant women, selenium reduced serum levels of TPOAb and prevalence of PPTD and permanent hypothyroidism (85, 86).

Omega-3-fatty acid supplements can diminish the inflammation associated with certain autoimmune disorders, so that they could be used to treat AIT (43).

Concerning food, small oily fish consumption was reported to cure and/or prevent autoimmune disorders, and improve certain maternal and neonatal outcomes (87, 88). Small oily fish are a source of long-chain polyunsaturated *n*-3 fatty acids, while large predator fish contain a number of pollutants (87). Recently, in a study on pregnant women with stable dietary habits who were sampled throughout gestation and day 4 postpartum, fish consumers had lower rates of positivity of both TPOAb and thyroglobulin Ab compared to meat eaters. Furthermore, within the fish-eater women, those consuming small oily fish had lower rates of either Ab compared to those consuming large fish. Hence, pregnant women should avoid consuming swordfish and increase consumption of oily fish (87, 88).

Therapy and Follow-up of PPT

As appropriately underscore (53), "treatment of PPT is based on clinical experience because there have been no trials comparing therapeutic alternatives."

In the thyrotoxic phase, if necessary, can be administered beta-blocker drugs, while antithyroid drugs are not recommended.

During the hypothyroid phase, symptomatic women could be treated with L-T4 at replacement doses and L-T4 therapy is recommended in hypothyroid women who are attempting pregnancy or who are breastfeeding. If treatment is not initiated, TSH dosage should be repeated every 4–8 weeks until thyroid function normalizes. L-T4 therapy should be continued for 12 months (42).

AUTHOR CONTRIBUTIONS

FDB, RG, MLD, RV, and SB designed the study and reviewed the literature on postpartum and thyroid autoimmunity. SB and FDB wrote the manuscript. All the authors have revised the paper and approved the final edition.

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OPINION
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Postpartum Mood Disorders and Thyroid Autoimmunity

Maria Le Donne[1], Carmela Mento[2], Salvatore Settineri[3], Alessandro Antonelli[4] and Salvatore Benvenga[5,6]*

[1] Unit of Gynecology and Obstetrics, Department of Human Pathology in Adulthood and Childhood "G. Barresi", University of Messina, Messina, Italy, [2] Department of Cognitive Sciences, Psychology, Educational and Cultural Studies (COSPECS), University of Messina, Messina, Italy, [3] Department of Biomedical and Dental Sciences and Morphofunctional Imaging (BIOMORF), University of Messina, Messina, Italy, [4] Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy, [5] Department of Clinical and Experimental Medicine, University of Messina, Messina, Italy, [6] Interdept. Program of Molecular & Clinical Endocrinology and Women's Endocrine Health, University Hospital Policlinico G. Martino, Messina, Italy

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INTRODUCTION

Because of the rapid emotional and endocrine changes in the postpartum period (1), postpartum mood disorders represent the most frequent form of maternal psychiatric morbidity (2–4). Postpartum mood disorders vary from a mild form of transient depression (maternity blues) to full-blown postpartum depression and severe psychosis (5, 6). Postpartum depression affects 10–30% of women within 1 year after delivery (7), and its risk is measurable already at 3 (8) or 7 days (2) postpartum. This risk predicts depression development in the following months (9, 10).

Thyroid function abnormalities exhibit comorbidity with various psychiatric disorders, including maternal depression. There are one-tenth of a million studies on mood disorders, but fewer than 5,000 (3.9% of almost 125,000) concern mood disorders in the postpartum period. Similarly, studies on autoimmune thyroid disease are almost 20,000, but only 72 (3.7% of 19,360) concern postpartum mood disorders and thyroid disorders, and merely 5 focus on postpartum mood disorders and thyroid autoimmunity. Thus, we hope that our opinion will stimulate interest.

POSTPARTUM AFFECTIVE DISORDERS AND THYROID DYSFUNCTION

Affective disorders and autoimmune thyroiditis are well known to affect women during puerperium. Up to 23% of all new mothers experiences thyroid dysfunction postpartum (11), compared with a prevalence of 3–4% in the general population (12). Maternal thyroid autoimmunity refers to the detection of thyroid autoantibodies against thyroperoxidase (TPOAb) and/or thyroglobulin (TgAb) in combination with normal thyroid function, and it has been reported to affect between 8 and 14% women in reproductive age (13). Concerning positivity for TPOAb, approximately 10% of pregnant women are TPOAb positive, and around one-third to half of them will develop postpartum thyroiditis (PPT) within 12 months after delivery (11, 14).

At least 2–3% of women have some form of thyroid dysfunction during pregnancy, and 10–17% of women have thyroid autoimmune disease despite euthyroidism (15, 16). Thyroid dysfunction in pregnancy is classified as (i) primary overt hypothyroidism (elevated TSH and a decreased FT4 during gestation with both concentrations outside the trimester-specific reference ranges) or subclinical hypothyroidism (with a TSH elevated beyond the upper limit of the pregnancy-specific reference range); (ii) hyperthyroidism (autoimmune Graves' disease or gestational transient thyrotoxicosis) (17); and (iii) positivity of thyroid autoantibodies, which increases the risk of thyroid dysfunction

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****Correspondence:***
Maria Le Donne
mledonne@unime.it

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following delivery and during the postpartum period. PPT is an inflammatory autoimmune condition, which occurs within the first year after delivery or miscarriage (a period when the immunosuppressive effect of pregnancy disappears), in women who were euthyroid prior to pregnancy (16, 18).

MOOD DISORDERS AND THYROID AUTOIMMUNITY IN GENERAL POPULATION

The association between subclinical hypothyroidism, with and without raised TPOAb, and well-being or depression is still controversial, in spite of many studies on this topic. Before moving to the abnormal setting, it is appropriate to mention the prevalence of thyroid autoantibodies in the general population and their association with mood disorders outside of the postpartum context.

An interaction between thyroid autoantibodies and mood disorders was first valuated in the early 1980s (19). Prevalence rates of thyroid autoantibodies in the general population vary widely, depending on several reasons, including sex and age distribution, geographic origin, variations in the cutoff level for antibody positivity (20–22). In an Italian survey, the overall prevalence of thyroid autoantibodies, using a cutoff of 1:100 for both microsomal antibodies and/or thyroid autoantibodies was 12.6% (females, 17.3%; males, 7.0%) (23). The reported prevalence in the United States healthy population was 13% for TPOAb (threshold at ≥0.5 IU/ml) and 11.5% for TgAb (threshold at ≥1.0 IU/ml) (21). Overall, the association of circulating thyroid autoantibodies with not otherwise specified mood disorders cannot be considered clearly established.

On the contrary, increased prevalence of circulating thyroid autoantibodies is shown in the following forms of mood disorders: treatment-refractory cases (24, 25), severe (26–28), atypical depression (29), anxiety disorders or mood disorders (30), and depression during early gestation, postpartum, and perimenopause (31–36).

In a population-based study, depression and anxiety were not associated with thyroid autoantibodies (37). In 2,049 subjects, autoimmune markers (TPOAb, anti-nuclear autoantibodies, and several other autoantibodies) were not associated with depression symptoms (38). Elevated TPOAb levels cannot be used as a general marker of poor well-being or depression, as shown in a large population-based Danish study of 8,214 individuals (39).

With regard to bipolar disorder, sample size was small in several studies (40–43). Offspring of bipolar subjects were found more susceptible to develop thyroid autoantibodies independently from the susceptibility to develop psychiatric disorders (44). Autoimmune thyroiditis was suggested as a possible genetic biomarker for bipolar disorder in a twin study (45). Hashimoto's encephalopathy can also occur with a bipolar disorder (46, 47), being vasculitis-related abnormalities in cortical perfusion one of the possible mechanisms (48). High levels of TPOAb were detected by Blanchin et al. (49) in the cerebrospinal fluid (CSF) of patients with Hashimoto's encephalopathy. Both sera from their patients and monoclonal TPOAb were able to link monkey cerebellar cells. Moreover, normal human astrocytes from primary cultures binded monoclonal TPOAb. The presence of antigenic targets for anti-TSH-receptor IgG on human cortical neurons and TgAb IgG in cerebral vasculature was described by Moodley et al. (50).

POSTPARTUM MOOD DISORDERS AND THYROID AUTOIMMUNITY

Risk for postpartum depression and alexithymia showed a direct borderline statistically significant correlation with serum TPOAb, suggesting that these mood disorders could be neurobehavioral consequences of an autoimmune attack (because of the TPOAb circulation in the CSF and of their possible cross-reaction with cerebral autoantigens) (3).

The PPT is more likely to occur in pregnant thyroid autoantibodies positive women compared to negative women (11). Most PPT women develop thyroid dysfunction during the first 6 months postpartum with initial mild symptoms of hyperthyroidism (heat intolerance, palpitations, weight loss, and fatigue) and a subsequent hypothyroid phase, frequently associated with depression (51). Approximately 50% of PPT women return euthyroid by 12 months PP (52).

Much uncertainty remains regarding the relationship between PPT and non-psychotic depression in thyroid autoantibodies positive euthyroid women. Harris et al. (53) found no difference in the rate of postpartum depression between thyroid autoantibodies positive women and thyroid autoantibodies negative women. However, the same author in 1992 reported an association between thyroid autoantibodies positivity and PPT (35). Subsequent studies on TPOAb positivity and postpartum depression in euthyroid women are controversial, founding no association (31, 54) or an association (34, 55). For instance, Kuijpens et al. studied prospectively 310 unselected women during gestation and up to 36 weeks postpartum (34). The presence of TPOAb was independently associated with depression at 12-week gestation and at 4 and 12 weeks postpartum (odds ratios between 2.4 and 3.8) in a prospective study on 310 unselected women (34).

A summary of the English-language literature in the last 25 years, which addressed the relationship between postpartum mood disorders and thyroid autoantibodies, is summarized in (**Table 1**).

In a follow-up study, Harris et al. (35) showed a significantly greater depression incidence in 110 thyroid autoantibodies positive women (47%) compared with 132 negative women (32%) regardless of thyroid dysfunction (**Table 1**). The same author in 2002 reported no difference in postpartum depression in TPOAb positive women treated with levothyroxine compared with TPOAb positive women given placebo and overall rates of major depression of 18.5% and depression in general of 38%, providing further evidence linking PPT and TPOAb positivity (60). No association was found between thyroid autoantibodies and postpartum mood disorders by Lambrinoudaki et al. (59). In another study, lower levels of serum FT3 were associated with increased incidence of mood disorders in the first postpartum week; only TPOAb and TgAb were significantly higher in women at risk for postpartum depression compared to women not at risk, using EPDS cutoff values of ≥13 or ≥14 (3). The presence of

TABLE 1 | Schematic comparison of the last 25 years studies on the relationship between postpartum mood disorders and thyroid autoantibodies.

Reference	(56)	(57)	(58)	(35)	(34)	(59)	(3)
Country	USA	USA	Sweden	United Kingdom	The Netherlands	Greece	Italy
No. of women	51	119	27	242	291	55	74
Age (years)	18 or older	18–45	Not specified	26.6–25.9	30.8–29.5	32.6 ± 4.2	31.8 ± 4.64
Pregnancy evaluation	Yes	Yes	No	Yes	Yes	No	No
Postpartum evaluation	Month 1	Month 6	Day 5, week 6,	Week 6–8	Weeks 4, 12, 20, 28, 36	Day 1–4, week 4–6	Day 3
Maternity blues scale (and cutoff)	Not evaluated	Not evaluated	Month 6	Not evaluated	Not evaluated	PBQ (≥8.2)	Not evaluated
Depression scale (and cutoff score)	EPDS (≥13)	POMS (>20)	EPDS (≥12)	RDC EPDS (≥13) Hamilton (≥15) HAS HDS (≥11)	Not specified	EPDS (≥11)	EPDS (≥13; ≥14) MADRS (≥15)
Depression score, mean ± SD			6.3 ± 4.8, 5.8 ± 4.4, 5.1 ± 4.7				EPDS: 8.45 ± 4.4 MADRS: 14.3 ± 12.3
Depression rate	16.36%	POMS-D: 10.9%	15.3% (day 5) 11.7% (week 6) 11.5% (month 6)	RDC depression 47% TAb+ vs 32% TAb−, major depression 16% TAb+ vs 11% TAb− Hamilton 18% TAb+ vs 13% TAb− EPDS 39% TAb+ vs 27% TAb− HAS 34% TAb+ vs 30% TAb− HDS 22% TAb+ vs 17% TAb−	59% TPOAb+ vs 38% TPOAb−	24.19% (week 1) 22.8% (week 6)	EPDS (≥13): 20.3%, EPDS (≥14): 13.5% MADRS: 30%
Thyroid function	TSH, FT3, FT4	TSH	TSH, FT3, FT4	TSH, FT3, FT4	TSH, FT4	TSH, FT3, FT4	TSH, FT3, FT4
Thyroid antibodies	TgAb, TPOAb	TPOAb	TPOAb	Tab (not specified)	TPOAb	TgAb, TPOAb	TgAb, TPOAb
Correlation of PPD with thyroid indices	EPDS, TSH ($P = 0.042$) EPDS, TAb not specified ($P = 0.043$)	POMS, TPOAb+ ($P = 0.023$) POMS-D, TPOAb+ ($P = 0.003$) POMS-A, TPOAb+ ($P = 0.013$)	EPDS, FT3 (OR = 0.8) EPDS, TSH (OR = 11.30) EPDS, TPOAb (no association)	Hamilton, TAb+ ($P = 0.0002$) EPDS, Tab+ ($P = 0.031$) HDS, TAB+ ($P = 0.003$)	PPD%, TPOAb+ ($P = 0.03$)	Mood score, FT4 (rho −0.3, $P \leq 0.05$) Mood score, TAb (no association)	EPDS, TPOAb[a] ($P = 0.056$) EPDS, TgAb ($P = 0.05$)

EPDS, Edinburgh Postnatal Depression Scale; GHQ, General Health Questionnaire; HAS, Hospital Anxiety Score; HDS, Hospital Depression Score; MADRS, Montgomery and Asberg Depression Rating Scale; OR, odds ratio; PBQ, Postpartum Blues Questionnaire; POMS, Profile of Mood States Scale (POMS-A, Anger; POMS-D, Depression); RDC, research diagnostic criteria; TgAb, thyroglobulin; TPOAb, thyroid autoantibodies against thyroperoxidase.

[a]Both TgAb and TPOAb levels were greater in depressed vs non-depressed women regardless of EPDS score threshold. Indeed, upon comparing score ≥13 vs score ≤12, TgAb was 38.5 ± 66.3 vs 16.6 ± 35.6 UI/ml ($P = 0.05$), and TPOAb was 26.2 ± 41.7 vs 10.5 ± 19.2 UI/ml ($P = 0.05$). Upon comparing score ≥14 vs score ≤13, TgAb was 29.9 ± 34.3 vs 19.7 ± 45.3 UI/ml ($P = 0.045$), and TPOAb was 34.3 ± 49.6 vs 10.5 ± 18.6 UI/ml ($P = 0.023$).

The rate of TPOAb positiveness in the 10 women with an EPDS score ≥14 was 6.4-fold greater than in 64 women with an EPDS score ≥13 (30.0 vs 4.7%, $\chi^2 = 7.437$, $P = 0.022$).

thyroid autoantibodies or higher TSH levels during the postpartum period may be related to depressive symptoms or dysphoric mood (56). Pregnant TPOAb positive women were shown to have higher depressive symptoms during pregnancy, and higher depression, anger, and total mood disturbance postpartum, regardless of the development of PPT (57).

Sylvén et al. (58) found an association between the TSH level over the clinical cutoff of 4.0 mU/l and the increased risk for depressive symptoms at 6 months postpartum in a Swedish population-based cohort (OR 11.30, 95% CI 1.93—66.11) (**Table 1**).

DISCUSSION

Tryptophan catabolites, indoleamine 2,3-dioxygenase, serotonin, and autoimmunity, as possible mediators of the immunoinflammation consequences and the oxidative and nitrosative stress, may induce postpartum depression (61).

In summary, there is scanty literature on the relationship between postpartum mood disorders and thyroid autoantibodies, with data available for the United States and a few European countries. Furthermore, these available data stem from differing methodologies (e.g., psychometric scales, thyroid autoantibodies assays, time and frequency of measurements). Nevertheless, a direct, positive, unfavorable relationship does appear. Also studies evaluating the relationship between thyroid autoantibodies' positivity and postpartum in euthyroid women have been mixed, with most of the studies demonstrating a significant association, confirmed also by a recent review of Dama et al. (62), who reported four of five studies finding a significant associations between TPOAb during gestation and postpartum depression (34–36, 57) and two of four studies finding links between postpartum TPOAb and depression (3, 34).

The cost-effectiveness of integrated perinatal mental health care has not been fully evaluated (63, 64) and is still controversial. The Edinburgh Postnatal Depression Scale (at a cut point of 16) had an incremental cost-effectiveness ratio (ICER) of £41,103 (€45,398, $67,130) per quality-adjusted life years (QALY) compared with routine care only. The ICER for all other strategies ranged from £49,928 to £272,463 per QALY vs routine care only, while the probability that no formal identification strategy was cost effective was 88% (59%) at a cost-effectiveness threshold of £20,000 (£30,000) per QALY. The major determinant of cost-effectiveness seems to be the potential additional costs of managing women incorrectly diagnosed as depressed (65). Leung et al. (66) showed that the use of EPDS as the screening tool and the provision of follow-up care had resulted in an improvement in maternal mental health at 6 months.

CONCLUSION

Negative emotions during pregnancy should be recognized using self-report questionnaires as Profile of Mood States Scale, to select women at risk for deflected postpartum mood and requiring psychological support. However, more research is required to clarify the predictive value and pathophysiological implications of the associations between TgAb and/or TPOAb positivity and postpartum depression and to support solid evidence of benefit and cost-effectiveness of a careful neuropsychological evaluation in more 10% of all pregnant women (positive for TPO or Tg antibodies).

Future research on postpartum mood disorders should target genetic variations of the deiodinases, thyroid hormone transporters, and identification of central nervous system-expressed targets of TPOAb (or other coexisting Ab which are specifically directed against these targets), particularly in CNS areas engaged in depression and/or alexithymia.

AUTHOR CONTRIBUTIONS

All the authors have participated in drafting and revising the manuscript submitted whose contents they approve.

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MINI REVIEW
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Thyroid Involvement in Hepatitis C Virus-Infected Patients with/without Mixed Cryoglobulinemia

Clodoveo Ferri[1], Michele Colaci[1], Poupak Fallahi[2], Silvia Martina Ferrari[2], Alessandro Antonelli[2] and Dilia Giuggioli[1]*

[1] Chair and Rheumatology Unit, Azienda Ospedaliero-Universitaria di Modena, Medical School, University of Modena and Reggio Emilia, Modena, Italy, [2]Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy

Thyroid involvement is a common condition that can be recorded during the natural course of different systemic rheumatic diseases, including the mixed cryoglobulinemia (MC) syndrome or cryoglobulinemic vasculitis. MC is triggered by hepatitis C virus (HCV) chronic infection in the majority of cases; it represents the prototype of autoimmune-lymphoproliferative disorders complicating a significant proportion of patients with chronic HCV infection. HCV is both hepato- and lymphotropic virus responsible for a great number of autoimmune/lymphoproliferative and/or neoplastic disorders. The complex of HCV-related hepatic and extrahepatic manifestations, including MC and thyroid involvement, may be termed "HCV syndrome." Here, we describe the prevalence and clinico-serological characteristics of thyroid involvement, mainly autoimmune thyroiditis and papillary thyroid cancer, in patients with HCV syndrome with or without cryoglobulinemic vasculitis.

Keywords: hepatitis C virus, thyroid, autoimmune thyroiditis, autoimmunity, cryoglobulinemia, cryoglobulinemic vasculitis, cancer, lymphoma

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Edited by:
Rauf Latif,
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Syed A. Morshed,
Icahn School of Medicine at Mount Sinai, United States

****Correspondence:***
Clodoveo Ferri
clferri@unimore.it

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INTRODUCTION

Autoimmune thyroiditis (AT) includes a group of thyroid diseases whose etiopathogenesis is characterized by chronic inflammatory response specifically self-directed against thyroid gland (1–3). Hashimoto's thyroiditis and Graves' disease represent the main pathophysiological and clinical entities of this single organ autoimmune disorder; nonetheless, subclinical thyroid dysfunctions should be considered in the disease spectrum (1, 2). Clinically, AT can lead to both hyper- and hypothyroidism, more often the latter, or it can produce slight, insidious variations of the TSH levels, without overt manifestations (1, 2). Presence of AT in the course of autoimmune systemic diseases, including mixed cryoglobulinemia (MC), is very frequent.

Mixed cryoglobulinemia is a small-vessel vasculitis due to vessel deposition of cryo- and non-cryoprecipitable IgG–IgM immune complexes (ICs) and complement, which represent the main pathogenetic mechanism of disease manifestations, such as palpable purpura of the legs, skin ulcers, peripheral polyneuropathy, or glomerulonephritis; moreover, arthralgias, fatigue, sicca syndrome are frequently associated (4–7). The abnormal production of ICs is determined by B cell clone proliferation triggered by hepatitis C virus (HCV) in a small proportion of infected patients (**Figure 1**, left). Besides its well-known hepatic tropism, HCV is able to infect several cell types (including B cells and thyrocytes); therefore, HCV lymphotropism can stimulate autoimmunity due to benign B-lymphocyte expansion or malignant B-cell non-Hodgkin's lymphoma [(5–7);

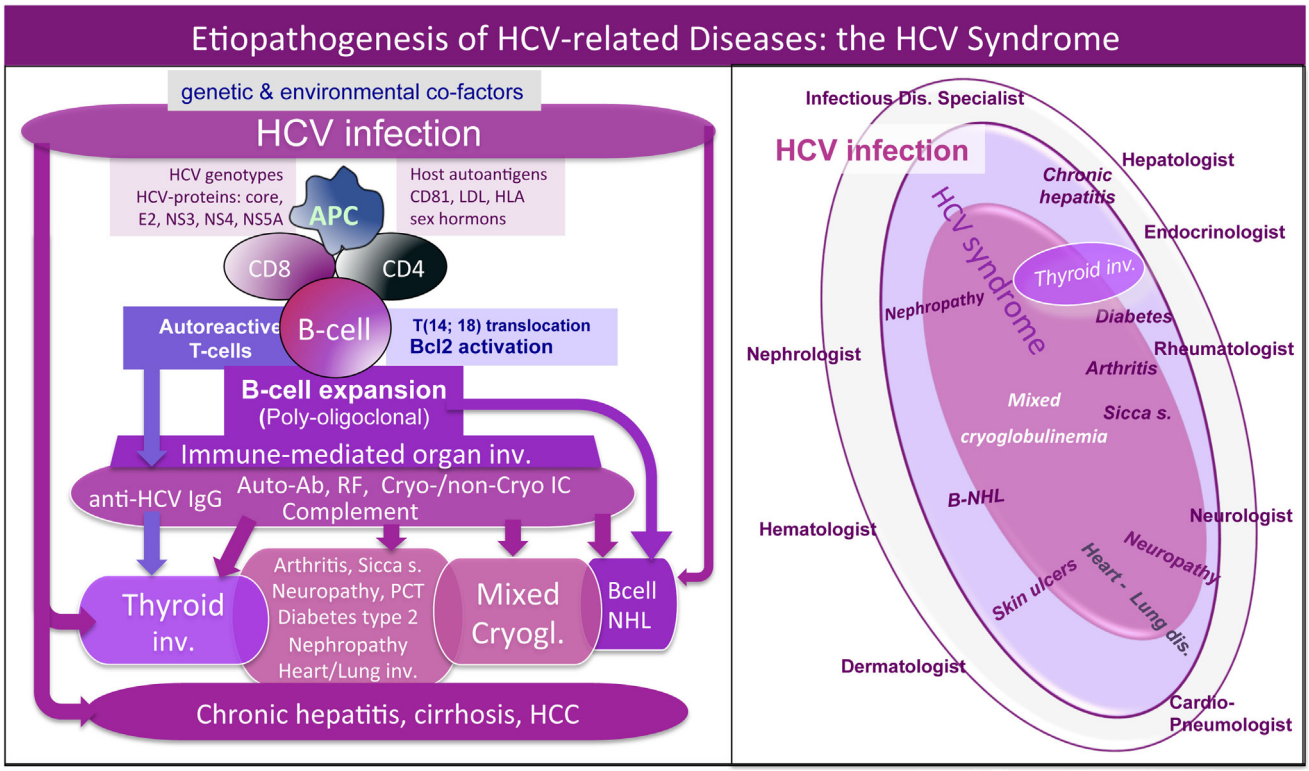

FIGURE 1 | Etiopathogenesis of hepatitis C virus (HCV)-related disorders and HCV syndrome. *Left*: the etiopathogenesis of HCV syndrome includes both hepatic and extrahepatic disorders. They may develop through a multifactorial and multistep process that includes chronic HCV infection, other potential environmental/toxic triggers, genetically driven host predisposition (particularly HLA alleles, metabolic, and/or hormonal factors), and complex cellular and molecular alterations. From one side, we can observe HCV-driven immune-system alterations with prominent "benign" lymphoproliferation and autoantibody production, from the other side, deeper oncogenetic alterations leading to frank B-cell neoplasias and other malignancies (B-NHL, HCC, and papillary thyroid cancer). These different pathogenetic mechanisms are not mutually exclusive; during long-term follow-up, we can assist in the same HCV-infected patient to the appearance of different organ- and non-organ-specific autoimmune/neoplastic diseases, among which thyroid involvement. HCV antigens (core, envelope E2, NS3, NS4, NS5A proteins) may exert a chronic stimulus on the host immune system. Important pathogenetic steps include high-affinity binding between HCV-E2 and CD81 and consequent *t*(14;18) translocation with bcl-2 proto-oncogene activation, cross-reaction between particular HCV antigens and host autoantigens (molecular mimicry mechanism), and direct cell infection by HCV responsible for neoplastic cell transformation. The "benign," often subclinical, B-cell proliferation with production of various autoantibodies, among which RF and cryo- and non-cryoprecipitable immune complexes may be frequently observed in chronically HCV-infected individuals. This condition may be the pathological substrate of various organ- and non-organ-specific autoimmune disorders, including thyroid involvement with/without mixed cryoglobulinemia (MC) syndrome or cryoglobulinemic vasculitis. Complicating malignancies can be observed in a small but significant percentage of patients, usually as a late complication of chronic HCV infection; moreover, both autoimmune and neoplastic disorders show a clinico-serological and pathological overlap. *Right*: schematic reproduction of the so-called "HCV syndrome" that encompasses the variety of HCV-related diseases. The majority of HCV-infected patients may remain totally asymptomatic or complicated by isolated liver involvement; however, a significant proportion of subjects may develop various extrahepatic manifestations that may include a variety of autoimmune/lymphoproliferative and neoplastic disorders; therefore HCV-positive patients are commonly referred to different specialists according the prevalent clinical manifestation(s). A number of HCV-infected patients may be referred early to the rheumatologist because of mild clinical manifestations such as arthralgias/mialgias, sicca syndrome, and/or RF seropositivity. MC syndrome, also termed cryoglobulinemic vasculitis, represents the prototype of extrahepatic, immune-mediated systemic disorder characterized by multiple organ involvement. In this scenario, HCV-related thyroid involvement is one of the most frequent manifestations, isolated or in association with other extrahepatic disorders, mainly cryoglobulinemic vasculitis. RF, rheumatoid factor; NHL, non-Hodgkin's lymphoma; HCC, hepatocellular carcinoma; PCT, porphyria cutanea tarda.

Figure 1, left]. Therefore, HCV patients frequently present a variable combination of different organ and/or systemic autoimmune diseases and neoplasias. The proposed "HCV syndrome" encompasses the complex of both hepatic and extrahepatic disorders [(7); **Figure 1**, right] among which the MC, also called cryoglobulinemic vasculitis, is the pathophysiological and clinical prototype (8).

As deeply described below, AT may be frequently found in HCV patients, with or without MC syndrome, suggesting an etiopathogenetic role of the virus in a subset of predisposed subjects (9–12).

THYROID DISEASE ASSOCIATED WITH HCV

Thyroid involvement is considered one of the most frequent endocrine disorders in association with chronic HCV infection, independently from the presence of MC (13); in particular, AT

may represent a frequent extrahepatic disease in the spectrum of HCV syndrome (4, 7, 13).

A large Italian population-based study published in 2004 (14) investigated the prevalence of AT (including thyroid dysfunction) in a series of 630 HCV patients not treated with interferon (IFN)-alpha, compared with three control groups: 389 individuals from an iodine-deficient area, 268 individuals from an area of iodine sufficiency, and 86 patients with chronic hepatitis B. HCV patients were more likely to have hypothyroidism (13%), anti-thyroglobulin antibodies (TgAb) (17%), and anti-thyroperoxidase antibodies (TPOAb) (21%) than the control groups (14).

A retrospective cohort study (15) analyzing data of users of US Veterans Affairs health-care facilities from 1997 to 2004 (146,394 HCV-infected patients vs. 572,293 HCV negatives) found that thyroiditis risk was slightly increased (adjusted hazard ratio 1.13, 95% CI 1.08–1.18; $p < 0.001$). It is supposable that the increased AT prevalence was underestimated because of 97% of cases were males, considering that both AT and hypothyroidism are associated with the female gender (12).

Other studies investigating the frequency of AT in smaller HCV patient cohorts were analyzed by Shen et al. in a recent meta-analysis of the world literature on the topic (16). Totally, 1,735 HCV-infected and 1,868 non-HCV subjects were pooled; prevalence of TgAb, TPOAb, and anti-thyroid microsomal antibody were 2.40-, 1.96- and 1.86-fold higher in HCV-positive subjects than in controls. Moreover, the hypothyroidism risk is 3.10 (95% CI 2.19–4.40) in HCV-infected patients.

Up to the recent introduction of new antivirals, the mainstay of HCV treatment was the IFN-alpha in combination with ribavirin. Several HCV patients developed AT as a consequence of IFN therapy, possibly due to the stimulation of antithyroid antibodies production in predisposed subjects (17). Frequently, IFN-related AT resolves within a few months (9).

THYROID DISEASE ASSOCIATED WITH MC

The coexistence of AT and MC has been reported in large cohort studies evaluating the clinico-serological characteristics of HCV-infected patients (15, 18). However, a definite association between these two diseases was first investigated by an Italian case–control prospective study (19), including 93 patients affected by HCV-related MC, 93 patients with isolated type C hepatitis, and 93 age/sex-matched healthy subjects from the same geographical area as controls. AT, subclinical hypothyroidism, and the presence of isolated specific serum autoantibodies, i.e., TPOAb and/or TgAb, were more frequent in the first group than the controls (35 vs. 16%, 11 vs. 2%, 31 vs. 12%, respectively). Moreover, higher frequency of AT was recorded among MC patients in comparison with hepatopathic patients (35 vs. 22%), with a significant high prevalence of TPOAb in MC (28 vs. 14%). Finally, hypothyroidism was associated with higher cryocrit and with the presence of other autoantibody positivity, as well as with longer MC duration, presence of proteinuria, or active hepatitis (19).

These findings showed that AT patients exhibited more pronounced autoimmune phenomena and severity of MC, which represents the prototype of autoimmunity in HCV patients (7).

Moreover, a longitudinal study investigating the incidence of AT during the follow-up of 112 MC patients vs. 112 matched controls was recently carried out (20). Of interest, the appearance of new cases of AT were evidenced during the course of HCV infection besides the observed AT at baseline; in particular, after a median of 67 and 96 months of follow-up in the two groups of HCV-positive patients with or without MC, AT was newly reported in 14 MC patients and in three controls; consequently, the overall prevalence of AT was increased up to 33 and 16%, respectively. Moreover, hypothyroidism that was invariably absent at baseline developed in 11 MC patients and three controls (subclinical in 9/11 vs. 2/3, respectively), while no cases of Grave's disease were registered. Interestingly, the logistic regression analysis confirmed that the appearance of hypothyroidism was related to female gender, a well-known risk factor for autoimmunity.

Noteworthy, even the prevalence of papillary thyroid cancer resulted higher in MC compared to hepatitis C patients; namely, the same study found two cases of cancer among MC patients, but none in hepatitis C and healthy controls (19). Subsequently, thyroid cancer was first reported also in patients with HCV infection regardless of the presence of other HCV-related manifestations (21); this finding supported the hypothesis of the oncogenic potential of HCV through the direct infection of thyrocytes with the possible contribution of the pathogenetic process responsible for AT (22, 23). Essentially, this latter reproduces the same multistep process already demonstrated for HCV lymphotropism with "benign" B-cell proliferation and subsequent lymphomagenesis (6, 7).

PATHOGENESIS

Clinico-epidemiological studies largely demonstrated that chronic HCV infection is a relevant risk factor for the development of a number of autoimmune or neoplastic diseases, including thyroid involvement, mainly AT (4, 5, 7–10). Considering this latter manifestation, an important contribute to understand the mechanisms involved in the pathogenesis of thyroid disorders was given by Blackard et al. (24), who demonstrated that HCV may infect a human thyroid cell line (ML1), which presents the membrane expression of the important HCV receptor CD81.

Furthermore, several studies by our group reported the upregulation of the CXCL9, CXCL10, CXCL11 chemokines, as well as IL-6 in the serum of MC patients who also presented AT (25–29). Therefore, it could be hypothesized that HCV may lead toward chronic stimulation of the immune system (**Figure 1**, left), namely the T-helper 1 lymphocytes, which secrete interferon-gamma and tumor necrosis factor-alpha, that in turn perpetuate the immune cascade increasing the levels of the chemokines cited above (**Figure 2**). Finally, the sustained activation of the immune system is at the basis of thyroid immune-mediated damage, leading to AT and other important disorders such as papillary thyroid cancer (21, 22).

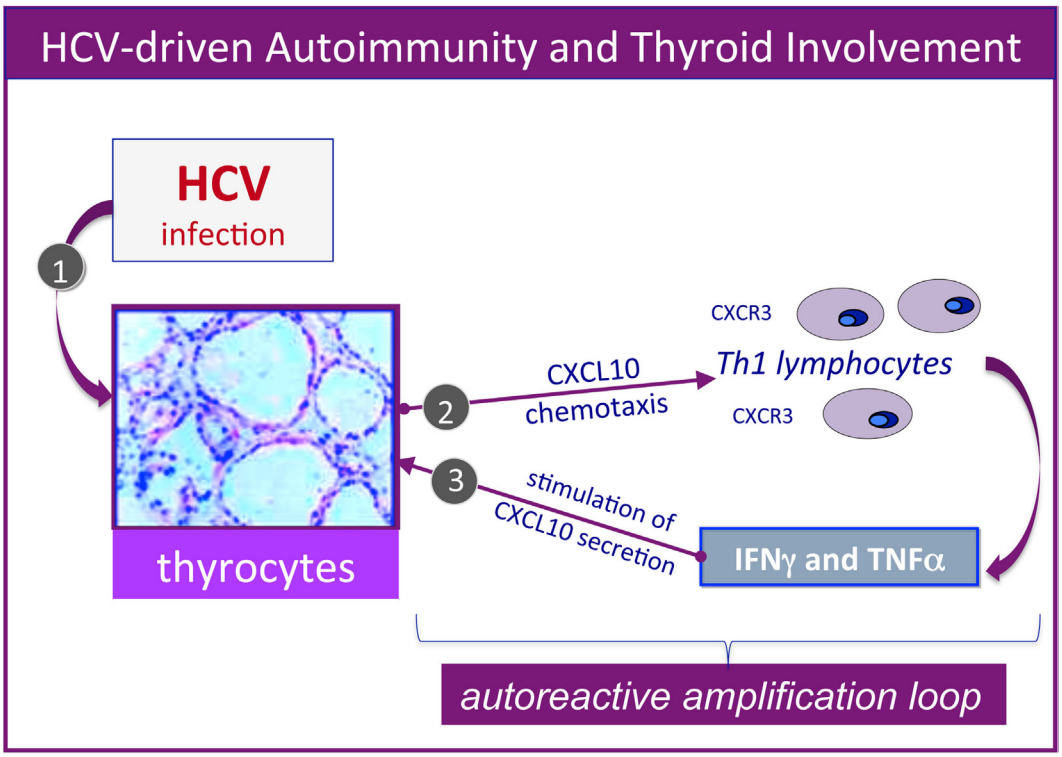

FIGURE 2 | Hepatitis C virus (HCV)-driven autoimmunity and thyroid involvement. Autoimmune thyroid involvement can be observed in a significant proportion of chronically HCV-infected patients; the possible etiopathogenetic mechanisms are schematically described in the figure. In genetically predisposed subjects, HCV thyroid infection (1) may lead to the upregulation of CXCL10 gene expression and secretion in thyrocytes (2); this chemokine may promote the recruitment of Th1 lymphocytes, which secrete interferon-γ (IFNγ) and tumor necrosis factor-α (TNFα). These cytokines may in turn induce CXCL10 secretion by thyrocytes (3), thus perpetuating the immune-mediated pathogenetic cascade. The consequence may be the appearance of thyroid disorders; a comparable pathogenetic mechanism may be hypothesized for HCV-driven diabetes type 2.

CONCLUSION

Autoimmune thyroiditis diagnosis is relatively simple and is based on typical laboratory and instrumental findings. The main autoantibodies of AT are the TPOAb and TgAb, while those directed against the TSH receptor are typical of Graves disease (1–3, 8). Histologically, lymphocytes infiltrate the thyroid parenchyma, even forming lymphoid follicles, progressively leading to parenchymal destruction and glandular fibrosis (3); anyway, thyroid biopsy is generally not required for the diagnosis. Instead, ultrasounds are usually important to support the AT diagnosis, identifying heterogeneous pattern of the gland, up to pseudo-nodular feature (1–3). The instrumental follow-up is obviously important to precociously diagnose the cases of thyroid cancer.

Considering the relative feasibility of AT diagnosis using not expensive or invasive exams, all HCV patients, mainly if affected by MC, should undergo thyroid evaluation periodically.

In the majority of MC patients, AT is a silent part of the clinical picture; otherwise, hypothyroidism, more frequently subclinical, may develop (9, 19, 20). The standard hormone replacement therapy is indicated in symptomatic HCV-associated AT with/without MC syndrome. HCV eradication is an important therapeutical/preemptive approach to several manifestations of HCV syndrome (30), including thyroid involvement, in particular the rare HCV-related papillary thyroid cancer.

AUTHOR CONTRIBUTIONS

CF: general revision and images drawing. MC: literature review and article writing. PF: literature revision. SF: literature revision. AA: general revision as regards endocrinology. DG: literature review and article writing.

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