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Sjögren's Syndrome and Autoimmune Thyroid Disease: Two Sides of the Same Coin

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Abstract

The coexistence of Sjögren's syndrome (SS) and autoimmune thyroid disease (AITD) has been documented. However, there is no consensus whether this coexistence should be considered as the same nosological condition or as polyautoimmunity. Thus, in this monocentric retrospective study, patients with SS alone (i.e., primary) were compared with patients with SS and AITD. In addition, a discussion of previous studies including those about genetic and environmental factors influencing the development of both conditions is presented. In our series, all patients with AITD had Hashimoto's thyroiditis (HT). No significant differences in age, gender, age of disease onset, and disease duration were found between the two groups. Lymphadenopathy and urticaria were more frequently registered in patients with SS-HT than in patients with SS alone ($p < 0.05$). Anti-Ro/SSA antibodies were more frequent in the primary SS group ($p = 0.01$). SS-HT patients were more likely to report a positive history of smoking ($p = 0.03$). The clinical expression of SS varies slightly when HT coexists. Although both entities share common physiopathological mechanisms as part of the autoimmune tautology, they are nosologically different and their coexistence should be interpreted as polyautoimmunity. Further studies based on polyautoimmunity would allow establishing a new taxonomy of autoimmune diseases.

Keywords Sjögren's syndrome · Autoimmune thyroid disease · Hashimoto's thyroiditis · Polyautoimmunity · Autoimmune diseases · Autoimmune tautology · Taxonomy

Abbreviations

AD	Autoimmune disease
AIH	Autoimmune hepatitis
AITD	Autoimmune thyroid disease
Anti-Tg	Anti-thyroglobulin antibodies
Anti-TPO	Anti-thyroperoxidase antibodies
APC	Antigen-presenting cell
EBV	Epstein-Barr virus
GD	Graves' disease
GEC	Glandular epithelial cells
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HSV	Herpes simplex virus
HT	Hashimoto's thyroiditis
HTLV-1	Human T cell lymphotropic virus 1
IQR	Interquartile range
MALT	Mucosal associated lymphoid tissue
MHC	Major histocompatibility complex
MSG	Minor salivary gland
OR	Odds ratio
RF	Rheumatoid factor
SES	Socioeconomic status
SLE	Systemic lupus erythematosus
SS	Sjögren's syndrome
SSc	Systemic sclerosis
Tg	Thyroglobulin
TPO	Thyroperoxidase
TSHR	Thyroid stimulating hormone receptor
VD	Vitamin D

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Introduction

Sjögren's syndrome (SS) is a chronic and systemic autoimmune disease (AD) characterized by a progressive lymphocytic and plasma cell infiltration of the salivary and lachrymal glands, accompanied by the production of autoantibodies leading to xerostomia and keratoconjunctivitis sicca (sicca symptoms) [1]. As we have mentioned, the spectrum of the disease may extend from an organ-specific autoimmune disorder (autoimmune exocrinopathy) to a systemic process involving the musculoskeletal, pulmonary, gastrointestinal, hematological, vascular, dermatological, renal, and nervous systems. Since the glandular epithelial cells (GEC) are the main target involved in the autoimmune process, SS is also known as "autoimmune epithelitis" [2, 3].

Most of the time, SS occurs without any other AD. In this case, the disease is still termed primary. SS can also occur in association with other AD (i.e., polyautoimmunity). The most frequent associations described have been with Hashimoto's thyroiditis (HT), rheumatoid arthritis (RA), and systemic lupus erythematosus (SLE) [4]. When this occurs, the disease is still designated secondary. Nevertheless, there is some confusion regarding this terminology. Some authors consider the coexistence of SS and organ-specific ADs including HT to be the same condition (i.e., primary SS) [3, 5].

Autoimmune thyroid diseases (AITD) are the most common organ-specific ADs, and affect around 10% of people worldwide [6, 7]. They are characterized by a T cell response against thyroid follicular cells [8]. Autoantibodies directed against thyroglobulin (Tg), thyroperoxidase (TPO) or the thyroid-stimulating hormone receptor (TSHR) are characteristic [6, 8]. Two main forms of AITD have been described: HT and Graves' disease (GD) [7], which are the major causes of hypothyroidism and hyperthyroidism, respectively [7]. HT is characterized by a Th1 immune response, with a T cell attack against the thyroid gland leading to thyroiditis and an overexposure to thyroid antigens, thus generating a secondary production of antibodies (anti-Tg and anti-TPO) [7, 9]. In GD, a Th2 response is the main immunological mechanism, in which anti-TSHR antibodies are a hallmark of disease [7, 9].

Current approaches to the understanding of pathophysiology of ADs are based on the interaction of genetic and environmental factors [10]. It is widely known that patients who develop one AD are at an increased risk of developing another one [10]. In fact, although ADs have particular symptoms and signs, studies have demonstrated the presence of shared immunopathogenic mechanisms supporting the development of polyautoimmunity [11, 12]. The prevalence of overt polyautoimmunity (i.e., two or more ADs in a single patient) has been estimated to be around 35% with AITD and SS being the ADs most frequently implicated [13].

Various studies have assessed the coexistence of SS and AITD [5, 14], and pointed out the fact that they share pathophysiological mechanisms [5]. However, there is no consensus about whether or not AITD is a distinct nosological condition differing from SS, and if the coexistence of these diseases should be considered polyautoimmunity (still named secondary SS) or the same entity [3, 5]. Therefore, our study analyzed patients with SS alone and with SS-HT. In addition, a comprehensive review of the genetic and environmental factors influencing their development is presented.

Materials and Methods

Study Population

This was a monocentric retrospective study in which 293 patients followed at the Center for Autoimmune Diseases Research (CREA) in Bogota, Colombia, were included. All subjects fulfilled the ACR/EULAR 2016 classification criteria for SS [15]. Patients presenting with SS alone were compared with those with SS-HT, defined by thyroid dysfunction (i.e., TSH >4.5 or <0.4 mIU/l) and the presence of anti-thyroid antibodies, as previously reported [16]. Thyroid ultrasound was not routinely done.

The patients' sociodemographic and cumulative clinical and laboratory data were obtained by interview, standardized report form, physical examination, and chart review as previously reported for other cohorts [16, 17]. The data were collected in an electronic and secure database.

Ethics Statement

This study was done in compliance with Act 008430/1993 of the Ministry of Health of the Republic of Colombia, which classified it as minimal-risk research. The institutional review board of the Universidad del Rosario approved the study design.

Sociodemographic Variables

Sociodemographic variables included information on gender, age, socioeconomic status, marital status, and occupation [18, 19] as previously reported [16, 17].

Clinical Variables

Clinical and laboratory variables were registered as present or absent at any time during the course of the disease as previously reported [16, 17].

Clinical variables assessed included age at symptom onset; first clinical manifestation; age at diagnosis [9, 20]; xerophthalmia, as previously defined as dry eye sensation lasting more than 3 months, foreign body sensation in the eyes, and use of artificial tears at a frequency higher than 3 times per day

[9, 15]; xerostomia defined as dry mouth sensation lasting more than 3 months or the need for liquids to swallow food [9, 15]; salivary gland compromise, defined as recurrent or persistent swelling of salivary glands [9, 15]; altered unstimulated salivary flow (1.5 ml in 15 min); and altered parotid sialography or altered salivary gammagraphy [15, 18]. A positive minor salivary gland biopsy was considered when the focus score was greater than 1 [15, 21, 22]. Anti-Ro/SSA and anti-La/SSB antibodies [9, 15, 22] were also assessed and evaluated as previously reported [16, 17]. A Schirmer's test was registered as positive or negative in each eye [15, 23].

Other manifestations evaluated included airway compromise (xeromycteria evidenced as recurrent sinusitis, dry throat, or the presence of epistaxis; xerotrachea evidenced as the presence of chronic non-productive cough; interstitial lymphocytic pneumonitis; pulmonary fibrosis; lymphoma; pleural thickening; pulmonary vasculitis; and pulmonary hypertension) [9]; renal impairment (tubulointerstitial and glomerulonephritis) [9]; musculoskeletal/constitutional manifestations such as arthralgia, arthritis, myalgia, parotid swelling, and lymphadenopathy [9]; cutaneous manifestations including urticaria, photosensibility, Raynaud's phenomenon, vasculitis, and cutaneous ulcers [9]; nervous system compromise, both central (white matter lesions, transverse myelitis, aseptic meningitis, optic neuritis, diffuse encephalopathy, or dementia) and peripheral (sensitive neuropathy, sensitive and motor neuropathy, polyradiculopathy, and autonomic neuropathy) [9]; and gastrointestinal manifestations including dysphagia, gastritis, and lymphoma.

A history of infections, exposure to organic solvents, toxics, silicone implants, coffee consumption, cigarette smoking, and use of psychoactive drugs, as well as a history of systemic diseases were also assessed as previously reported [16, 17]. Concerning pharmacological treatment variable was not taken into consideration for the purpose of this analysis.

Statistical Analysis

Univariate and bivariate analyses were done. Categorical variables were analyzed by frequencies. Results are reported in percentages as well as in median and interquartile range (IQR). The data were analyzed using χ^2 and the Kruskal-Wallis tests. Statistical analyses were done by using the statistical program R v.3.4.4.

Results

Of the 293 patients, 94.8% were women. There were 161 patients with SS alone, 26 with SS-AITD, and 106 with other combinations of polyautoimmunity, including RA, SLE, and SSc observed in 52 (17.7%), 50 (17.1%), and 13 (4.4%) patients respectively. All patients with AITD were diagnosed with HT and none of them with GD. Multiple autoimmune syndrome [24] (i.e., patients with three or more ADs) was observed in 34 (11.6%) patients. Patients with SS alone (i.e., primary) were compared with those presenting SS-HT.

Sociodemographic and clinical characteristics of SS alone and SS-HT patients are shown in Table 1. All patients with SS-HT developed HT after SS. More SS-HT patients reported ever smoked ($p = 0.03$) as well as coffee intake history ($p = 0.03$). Anti-Ro/SSA positive results were significantly more frequent among patients with SS alone ($p = 0.01$). As expected, the frequency of positive anti-thyroid antibodies (anti-TPO and anti-Tg) was significantly higher among SS-HT patients ($p < 0.001$). Patients with SS alone showed a lower prevalence of lymphadenopathy than SS-HT ($p = 0.02$). There were no differences in parotid swelling and persistent parotid swelling between the two groups.

There were two patients with pulmonary fibrosis in the group with SS alone, and one patient with pulmonary hypertension in the SS-HT group. As there were no patients diagnosed with lymphoma, tubular acidosis, pulmonary vasculitis, or pleural thickening in neither the SS nor the SS-HT groups, these variables were excluded from the analysis and are not reported in Table 1.

Discussion

Our results disclosed overt thyroid polyautoimmunity in 15.7% and latent thyroid polyautoimmunity (i.e., the presence of anti-thyroid antibodies in euthyroid SS patients) in 5.6% of patients with SS. The coexistence of HT did not have a major effect on SS, except for the presence of lymphadenopathy and urticaria, which were not associated with cigarette smoking (Table 1).

Several studies have assessed the prevalence and clinical characteristics of patients presenting with SS-HT. Table 2 summarizes the most important findings of such studies [10, 25–44]. The 15.7% prevalence of overt thyroid polyautoimmunity in SS observed in our series (Table 2) is similar to the one reported by several other authors [31, 32, 36, 38, 42, 44]. A recent review of the epidemiological, clinical, and pathological characteristics of overt thyroid polyautoimmunity in SS reported a prevalence of SS-HT ranging from 10 to 30% [14]. We have previously reported HT as the most common form of polyautoimmunity in SS [10]. HT may coexist with other several ADs, including RA and SLE [5, 13].

No significant differences were observed regarding age and disease duration between SS and SS-HT. Zeher et al. [26] reported an average time lag of 5.5 years between the diagnosis of SS and HT, and suggested that both HT and GD are more likely to follow SS. Our results show that patients with

Table 1 General characteristics of patients with SS alone (i.e., primary) and SS-HT

Variable	SS ($n = 161$)	SS-HT ($n = 26$)	p value
Female (%)	155 (96.2)	25 (96.1)	1
Age, years (IQR)	54 (44.5–61)	52 (45.5–60.2)	0.95
Age of disease onset (IQR)	45.5 (37.7–54)	45.5 (35.7–54)	0.6
Disease duration, years (IQR)	2 (0–7)	6.5 (4–12.7)	0.42
Socioeconomic status (%)			0.68
Low	21/124 (16.9)	6/25 (24)	
Medium	52/124 (41.9)	9/25 (36)	
High	51/124 (41.1)	10/25 (40)	
Cigarette smoking, ever (%)	39/133 (29.3)	12/22 (54.5)	0.03
Coffee intake, ever (%)	101/127 (79.5)	23/24 (95.8)	0.1
Coffee intake (%)[a]			0.03
Occasional	26/127 (20.5)	1/24 (4.1)	
Low	7/127 (5.5)	2/24 (8.3)	
Medium	39/127 (30.7)	4/24 (16.7)	
High	42/127 (33.1)	10/24 (41.7)	
Former consumer	13/127 (8)	7/24 (29.2)	
History of infectious disease (%)	13/143 (9.1)	2/25 (8)	1
History of exposure to toxics (%)	74/142 (52.1)	13/24 (54.2)	1
Cardiovascular disease (%)	37/143 (25.9)	5/25 (20)	0.7
Clinical manifestations (%)			
Xerophthalmia	150/150 (100)	25/26 (96.1)	0.88
Xerostomy	153/154 (99.4)	26 (100)	1
Xeromycteria	70/159 (44)	16 (61.5)	0.14
Xerotrachea	27/159 (17)	5 (19.2)	0.99
Urticaria	25/159 (15.7)	12 (46.1)	< 0.001[b]
Photosensitivity	48/159 (30.2)	10 (38.5)	0.53
Raynaud phenomenon	39/159 (24.5)	6 (23.1)	1
Vasculitis	8/159 (5)	2 (7.7)	0.92
Cutaneous ulcers	4/159 (2.5)	0 (0)	0.92
Glomerulonephritis	2/159 (1.2)	0/25 (0)	1
Arthralgia	121/159 (76.1)	18 (69.2)	0.61
Arthritis	47/159 (29.5)	10 (38.5)	0.49
Myalgia	67/159 (42.1)	14 (53.8)	0.36
Parotid swelling	26/159 (16.3)	8 (30.7)	0.13
Persistent parotid swelling	2/159 (1.2)	1/25 (4)	0.87
Lymphadenopathy	19/159 (11.9)	8 (30.7)	0.02[b]
Peripheral neuropathy	14/158 (8.9)	3 (11.5)	0.94
CNS compromise	3/158 (1.9)	0 (0)	1
Dysphagia	38/159 (23.9)	8 (30.8)	0.61
Gastritis	63/159 (39.6)	14 (53.8)	0.25
Splenomegaly	2/159 (1.2)	2 (7.7)	0.17
Sialography, positive (%)	16/29 (55.1)	7/9 (77.8)	0.41
Salivary flow, positive (%)	47/95 (49.5)	10/18 (55.5)	0.82
Schirmer's test, positive (%)	89/100 (89)	17/20 (85)	0.89
MSG biopsy, positive (%)	148 (91.9)	24 (92.3)	1
ANAs (%)	119/124 (96)	22/22 (100)	0.74
Anti-Ro/SSA (%)	103/127 (81.1)	14/25 (56)	0.01
Anti-La/SSB (%)	62/114 (54.4)	10/25 (40)	0.27
Anti-TPO (%)	7/21 (33.3)[c]	22 (84.6)	< 0.001
Anti-Tg (%)	5/33 (15.1)[c]	13/20 (65)	< 0.001
Rheumatoid factor (%)	50/79 (63.3)	4/10 (40)	0.28

SS, Sjögren's syndrome; *HT*, Hashimoto's thyroiditis; *IQR*, interquartile range; *MSG*, minor salivary gland; *ANAs*, anti-nuclear antibodies; *CNS*, central nervous system; *Anti-TPO*, anti-thyroperoxidase antibodies; *Anti-Tg*, anti-thyroglobulin antibodies

[a] Coffee intake was asked as yes or no, and measured in cups per day (i.e., 1, current low; 2–4, current medium; and > 4, current high)

[b] None of these variables were associated with cigarette smoking

[c] There were 9 (5.6%) patients with SS presenting with latent thyroid polyautoimmunity, of whom 3 had both anti-TPO and anti-Tg antibodies, 4 had only anti-TPO, and 2 had only anti-Tg. None of them with goiter

Table 2 Prevalence and characteristics of AITD in SS

Study	Patients (*N*), Origin	Prevalence, number (%)				Comments
		Thyroid dysfunction	HT	GD	Non-autoimmune thyroid disease	
Karsh et al., 1980 [25]	23 USA	19 (82.6)	NR	NR	NR	Anti-TPO and anti-Tg antibodies were reported in 41.6% and 21.7%, respectively.
Kelly et al., 1991 [36]	100 England	14 (14)	11 (11)	3 (3)	0 (0)	
Hansen et al., 1991 [38]	28 Sweden	5 (18)	5 (18)	NR	NR	Anti-Tg and/or anti-microsomal antibodies were present in 36% of patients.
Bouanani et al., 1991 [33]	26 France	8 (30.7)	NR	NR	NR	
Foster et al., 1993 [39]	42 England	NR	NR	NR	NR	Anti-TPO and anti-Tg antibodies were reported in 33% and14.3%, respectively.
Pérez-E et al., 1995 [40]	33 Mexico	15 (45)	8 (24)	2 (6)	5 (15)	
Punzi et al., 1996 [32]	121 Italy	NR	16 (13.4)	NR	NR	SS and thyroid diseases were less likely to have positive ANAs and RF.
Davidson et al., 1999 [30]	74 England	NR	12 (16.2)	NR	NR	HT was highly prevalent among seronegative SS patients.
Ramos-Casals et al., 2000 [41]	160 Spain	58 (36)	11 (18)	2 (1)	26 (16)	
D'Aborneau et al., 2003 [42]	137 France	21 (15.3)	20 (14.6)	1 (0.7)	9 (6.6)	In SS patients, RF ($p < 0.03$) and anti-Ro/SSA antibodies ($p < 0.05$) were more frequent, and anti-Ro/SSA reactivity was more frequent in SS patients who then developed thyroid dysfunction ($p < 0.04$).
Tunc et al., 2004 [43]	53 Turkey	NR	NR	NR	NR	In this case-control study, there was no association between primary SS and AITD.
Lazarus et al., 2005 [31]	114 England	18 (15.8)	16 (14)	2 (1.8)	NR	
Biró et al., 2006 [44]	400 Hungary	55 (13.8)	28 (7)	12 (13)	NR	The most common coexistent AD with HT and GD, when evaluated from the reverse point of view, was SS.
Zeher et al., 2009 [26]	479 Hungary	95 (19.8)	30 (6.2)	18 (3.7)	10 (2)	SS preceded HT by 5.5 years in 50% of cases. In GD, clinical and immunoserological status did not significantly differ between patients with or without SS.
Mavragani et al., 2009 [27]	54 Greece	NR	NR	NR	NR	The prevalence of sicca symptoms in SS patients was similar to those patients who did not fulfill criteria for SS.
Amador-Patarroyo et al., 2012 [10]	410 Colombia	88 (21.5)	NR	NR	NR	
Malladi et al., 2012 [35]	886 Argentina, China, Denmark, Japan, UK, India, USA	68 (7.7)	47 (5.3)	21 (2.4)	NR	
Lu et al., 2013 [28]	389 Taiwan	81 (20.7)	NR	NR	NR	Thyroiditis and unspecified hypothyroidism were found to be significantly associated with SS. A time lag of around 6 years existed between SS and thyroid disorders.
Caramaschi et al., 2013 [34]	100 Italy	NR	27 (27)	NR	NR	Patients with SS-AITD have a milder clinical phenotype of SS and lower risk factors for developing lymphoma.
Abrol et al., 2014 [29]	152 UK	24 (15.8)	NR	NR	NR	Non-Hodgkin lymphoma occurred in 10.5% of patients.
Lockshin et al. 2015 [37]	157 USA	20 (12.7)	NR	NR	NR	Patients with SS polyautoimmunity differ in etnicity.
Current series	293 Colombia	46 (15.7)*	46 (15.7)	0 (0)	0 (0)	

Data correspond to number of patients (%). *Anti-TPO*, anti-thyroperoxidase antibody; *Anti-Tg*, anti-thyroglobulin antibody; *RF*, rheumatoid factor; *ANA*, anti-nuclear antibody; *HT*, Hashimoto's thyroiditis; *GD*, Graves' disease; *NR*, not reported

*There were 46 patients (15.7%) with HT and SS as part of polyautoimmunity, including multiple autoimmune syndrome (i.e., three or more ADs), but only 26 with SS-HT

SS-HT evince a condition similar to SS alone. Previous reports suggested that SS-HT patients could present milder symptoms than SS alone [14, 34]. Variations in the clinical characteristics and manifestations of ADs have been described as an effect of

age [45]. Although both AITD and SS are more frequent among adult patients, AITD may develop in younger people at a higher frequency than SS does [9]. This fact explains, in part, the higher frequency of polyautoimmunity observed in AITD patients.

The following is a listing of the similarities and differences between SS and AITD. All salivary glands derive from growths of oral epithelium into the mesenchyme [46]. The ductal system and the secretory system arise from the epithelial overgrowths. However, in parotid, submandibular and sublingual glands, they have an ectodermal origin while in minor salivary glands, they have both endodermal and ectodermal origin [46]. As mentioned by Nilsson and Fagman, "the thyroid gland forms as a proliferation of endodermal epithelial cells on the median surface of the developing pharyngeal floor" [47]. These progenitors give rise to the follicular cells that form the thyroid follicles composed of thyrocytes, which are considered epithelial cells [47].

There is evidence of the common pathophysiological characteristics shared by SS and AITD [14]. Both diseases are characterized by the presence of lymphocytic infiltrates, especially CD4+ T lymphocytes and B cell activation [5]. The role of epithelial cells in tissue inflammation and the presence of specific chemokines such as CXCL10 have been described in AITD as markers of inflammatory response leading to tissue destruction while in SS, it has been demonstrated that epithelial cells produce CXCL9 and CXCL10 and thus contribute to salivary gland damage [14, 48].

GEC (i.e., salivary and lachrymal) are considered as the starting point in the pathogenesis of SS [48, 49]. An increased expression of the class II molecules of the major histocompatibility complex (MHC) confers the characteristic of non-professional antigen-presenting cells (APC) on them. Antigen presentation leads to the production of Th1 cytokines [48]. Various proinflammatory molecules such as CXCL13, CCL17, CCL19, CCL21, and CCL22 mediate dendritic cell infiltration while the production of IFNγ mediates the secretion of CXCL9 and CXCL10 that favor T cell migration to the salivary glands while CXCL13 directs B cell movement into the glands and further formation of lymphoid structures [48]. Immune regulation through the NFκB pathway appears to be impaired in SS as a consequence of a defective function of IkB and TNFAIP3 [48, 49]. Ro and La antigens are released in apoptotic bodies and exosomes after GEC apoptosis. IFNγ and IFNα play an important role in the pathogenesis of SS as they mediate B cell and T cell infiltration of salivary glands, activate lymphocytes, induce expression of MHC, and promote autoantibody production [48]. In summary, SS is characterized by a Th1 response in the early stages which turns progressively into a Th2 condition as the disease progresses [49] (Fig. 1).

In AITD, T cell migration to the thyroid gland plays an important role in the pathogenesis of both HT and GD [8]. Thyroid follicular cells, as non-professional APC, present epitopes of thyroglobulin to T cells through class II MHC molecules [50]. Depending upon the cytokine milieu, a Th1, Th2, or Th17 response is initiated [50, 51]. The thyroid gland appears to have a characteristic Th1 and Th17 infiltrate, especially CD8+ T cells, resulting in chronic inflammation and apoptosis (Fig. 1). A decreased sensitivity of CD4+ T cells to the inhibitory effect of TGFβ has been described [8]. HT is characterized by a higher concentration of CD8+ cells in thyroid gland [50]. After immunogenic stimuli, the normal balance between T regulatory cells (T-reg) and auto-reactive T cells is disrupted. Thus, a break in immune tolerance is generated leading to an autoimmune process [8, 51]. Proinflammatory cytokine CXCL10 induced by IFNγ appears to play an important role during early stages of thyroiditis as it recruits Th1 cells that upregulate the production of IFNγ through CXCR3 expression [51]. As in SS, there is evidence that cell apoptosis is one of the most important mechanisms implicated in tissue destruction, and it is thought to be caused by variations in the expression of Fas/FasL [8, 50].

The genetic factors play an important role in the development of ADs. Over the last decade, genome-wide association studies (GWAS) have identified several gene variations associated with ADs, most of them within the HLA region [52]. Several studies have assessed the genetic characteristics of SS and AITD and have described common HLA molecules expressed by thyroid and epithelial cells such as HLA-B8 and HLA-DR3 [14, 53, 54]. Figure 2 summarizes the genes incriminated in the two diseases through GWAS [55–65]. Although the genetic factors contributing to the pathogenesis of SS are not fully known, recent GWAS described non-HLA genes such as *BLK*, *TNFAIP3*, *DDX6-CXCR5*, *COL11A2*, *STAT4*, *IRF5*, *TNPO3*, *TNIP1*, *FAM167-BLK*, *GTF2I*, and *IL12A* as being associated with SS [55, 62–64, 66]. Most of the latest GWAS studies have disclosed genes involved in innate and adaptive immunity [67]. The previously mentioned genes are involved in the increase in IFN signaling, cytokine production, B cell function, and antibody production, through the NFκB pathway [63, 68, 69]. In a previous meta-analysis, *HLA-DQA1*05:01*, *HLA-DQB1*02:01*, and *HLA-DRB1*03:01* alleles were found to be risk factors for SS. Conversely, the *HLA-DQA1*02:01*, *HLA-DQA1*03:01*, and *HLA-DQB1*05:01* alleles were found to be protective factors [70].

Genetic studies for GD and HT have evaluated the role of HLA genes and non-HLA genes such as *CTLA-4*, *PTPN22*, *FCRL3*, *CD25*, and *CD40* [53, 71–74]. *CTLA-4* is a costimulatory molecule expressed on T cells, including T-reg cells where it plays an important role in their suppressive function [71]. A lower function of this gene has been described in AITD [71]. *PTPN22*, a common autoimmune gene, influences the susceptibility to both GD and HT [53, 71, 72, 75]. *CD40* has been associated with GD. It plays a crucial role

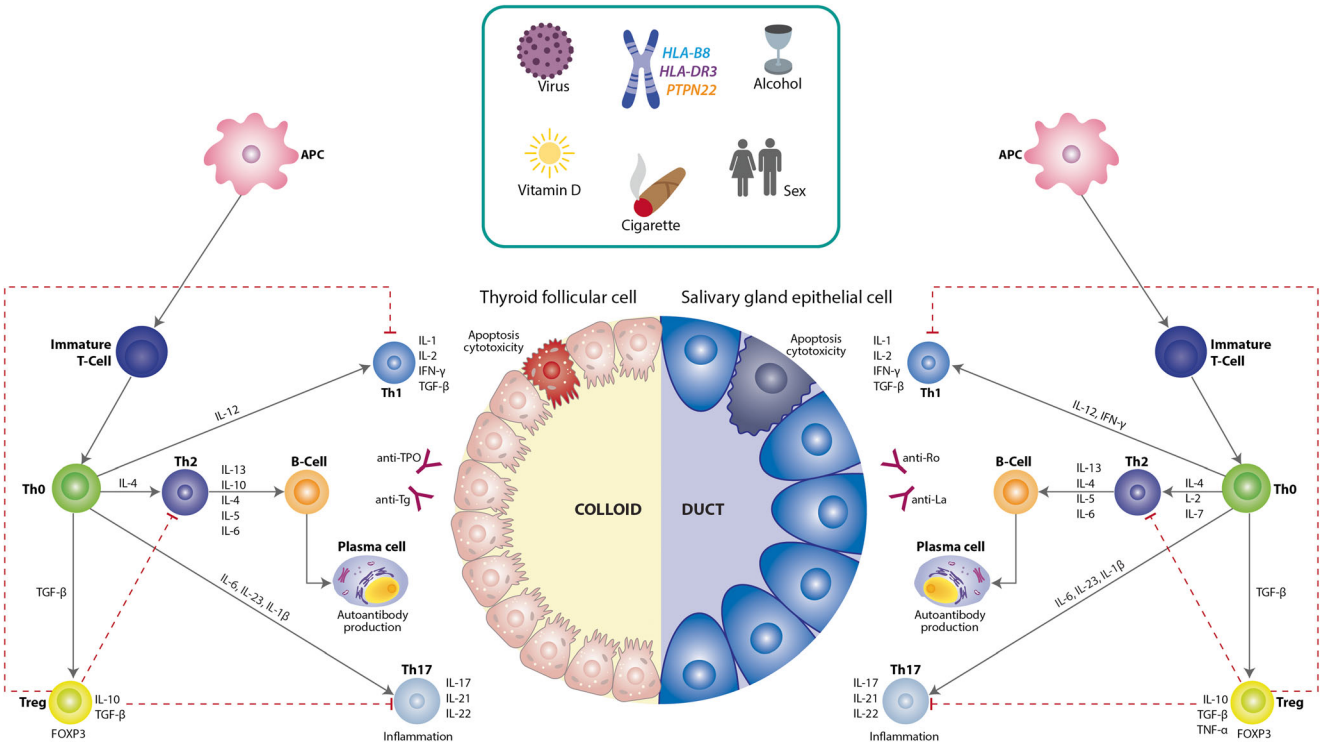

Fig. 1 Common pathophysiological mechanisms in SS and HT. Association studies have identified several susceptibility genes for SS and AITD including *HLA-B8*, *HLA-DR3*, and *PTPN22*. Environmental factors have been described as protective or risk factors for the development of ADs. Previous viral infections such as herpes simplex virus, Epstein-Barr virus, human T cell lymphotropic virus 1, and hepatitis C virus have been associated with both SS and AITD. Evidence of the role of vitamin D (VD) in the development of SS and AITD is scarce and has shown contrasting results. However, a protective effect of VD on many other ADs has been described. Cigarette smoking seems to play a protective role in SS and AITD, although the evidence is not unanimous and the immunopathological mechanisms are not fully understood. Evidence regarding the influence of consumption of alcohol in SS is scarce, while a low-to-moderate alcohol consumption has been associated with a lower risk of developing AITD. The effect of environmental factors on genetically susceptible individuals leads to the loss of immunological tolerance toward thyroid follicular cells and epithelial cells in exocrine glands. Non-professional antigen-presenting cells (APCs) interact with immature T cells leading to their differentiation into Th0 cells, which differentiate into Th1, Th2, Th17, or T-reg cells depending on the cytokine milieu. Thyroid follicular cells and salivary (or other exocrine) epithelial cells act as non-professional APCs. Th1 cells mediate apoptosis and cytotoxicity of thyrocytes and glandular epithelial cells. Furthermore, Th2 cells differentiate into plasma cells with the consequent production of autoantibodies directed toward thyroperoxidase (anti-TPO) or thyroglobulin (anti-Tg) in HT or anti-Ro and anti-La antibodies in SS. Th17 cells mediate inflammation by the production of proinflammatory cytokines. A decrease in T-reg number and function has been described as playing an important role in the pathogenesis of both diseases

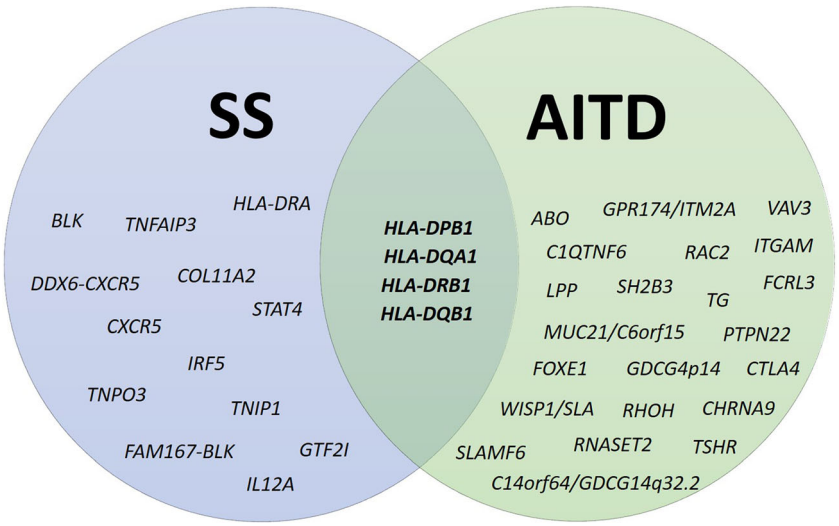

Fig. 2 Venn diagram of associated genes with SS and AITD. The diagram shows susceptibility genes identified by the main genome-wide association studies (*p* value 5.0E-08) [55–65]. Other association studies have found additional common polymorphism at *PTPN22*, *CTLA4*, and *IL10* genes among others (see text for details)

in the interaction between APC and T cells while in B cells, it promotes their proliferation and production of immunoglobulin G [53, 71]. Among the HLA alleles, GD has been associated with *DQA1*0501* [72] while HT has been associated with *DRB1*03*, *DRB1*04*, *DRB1*08*, *DQB1*04*, *DQB1*0301/4*, *DQA1*03011/12*, and *DQA1*0401* in Caucasians [76]. Several other susceptibility loci associated with HT and GD such as *IL2RA*, *BACH2*, *FOXE1*, *FOXP3*, *MMEL1*, *TRIB2*, *and ITGAM* and thyroid specific genes *TSHR* and *TG* have been described [53, 73, 77]. Genes influencing AITD can be classified as thyroid-specific or immune-modulating genes with an important role in immune tolerance and T lymphocyte activation [78].

The role of environmental factors in the susceptibility to ADs has been widely studied [19, 79]. Several factors such as coffee intake, cigarette smoking, alcohol intake, serum VD levels, previous infections, and gut microbiota influence the risk of developing ADs as well as their severity [19, 79] (Fig. 1). Socioeconomic status (SES) has been described as a key variable influencing the prevalence of ADs [19]. The effect of SES in SS is not unanimous. A significant association between low SES and low educational level with polyautoimmunity was found in the Colombians [10] while in Swedish patients, no significant effect of SES and educational level on SS was reported [80]. Results from a recent study comparing SS patients with non-Sjögren's sicca patients found no association of SES or educational level with SS [81]. Data from the current study showed no significant differences in SES and educational level between SS alone and SS-HT.

Our results also showed a higher prevalence of cigarette history (ever smoking) in SS-HT patients. Cigarette smoking has been associated with an increased risk of developing multiple sclerosis, RA, AITD, SLE, and primary biliary cholangitis [19, 79]. Evidence on the effect of tobacco smoking on SS is controversial [79]. A case-control study including 63 SS cases and 252 controls showed that "the status of current smoker at entry was associated with a lower risk of being diagnosed with SS compared with non-smokers, while former smoking was associated with a higher risk of being diagnosed with SS compared to never smoking and current smoking" [80]. In addition, no differences were found in autoantibodies based on smoking status [80]. A recent study comparing 587 SS patients with 701 patients with non-Sjögren's sicca found a lower risk of being classified as SS in current smokers vs former smokers and in ever smokers vs never smokers [81]. Authors found significant differences between smokers and non-smokers since current smokers evidenced a lower risk of showing anti-Ro/SSA antibodies, hypergammaglobulinemia, and a focus score > 1 in the minor salivary gland biopsy [81]. A population-based twin case-control study found that smoking was associated with an increased risk of developing thyroid disease [82]. When evaluating autoimmune and non-autoimmune thyroid disease, the results maintained significance [82]. Wiersinga has reviewed the role of smoking and other environmental factors with respect to the risk of developing AITD [73, 83]. He highlighted an increased risk of GD in current smokers and a relatively protective role against hypothyroidism as current smokers had lower prevalence of anti-TPO antibodies and lower prevalence of latent and overt hypothyroidism [73].

Coffee consumption has opposite effects among various ADs as seems to be associated with a lower risk of multiple sclerosis and ulcerative colitis while it has been associated with a high risk for the development of RA and SLE [79]. Evidence about the role of coffee in SS and AITD is scarce. In a recent review, Shariff et al. [84] indicated that there is a lack of studies "specifically examining the etiological relationship between coffee consumption and thyroid disease onset in humans." Our results showed significant differences in the pattern of coffee consumption between SS and SS-HT; nevertheless, a history of coffee consumption or current coffee consumption showed no differences between groups. Sample size and a possible memory bias precluded a conclusion about the influence of coffee intake on the development of SS-HT.

Although the history of infections, exposure to organic solvents, and use of psychoactive drugs was assessed in the current study, none of them showed significant differences between SS and SS-HT patients. The role of previous infections on the pathogenesis of ADs has been widely studied [19]. AITD has been associated with a history of viral and bacterial infections as well as with an exposure to environmental toxics [85]. GD has been linked with herpes simplex virus (HSV), rubella, mumps virus, Epstein-Barr virus (EBV), human immunodeficiency virus (HIV), and human T cell lymphotropic virus 1 (HTLV1) while HIV, hepatitis C virus (HCV), and parvovirus B19 have been associated with AITD in general [86]. As has been shown in AITD, EBV, HTLV1, and HSV have been associated with the pathogenesis of SS [87]. Brito-Zerón et al. [87, 88] have discussed the high prevalence of HCV identified in SS patients and the link to a predominance of anti-La/SSB rather than anti-Ro/SSA response.

Alcohol consumption and VD appear as two widely studied factors in ADs. The current study did not assess alcohol consumption nor VD levels. However, there is evidence that points low-to-moderate alcohol consumption as a protective factor for the development of RA and SLE [79]. As reviewed by Wiersinga [73], two studies in Denmark showed that moderate alcohol consumption was associated with a lower risk of overt HT and GD [89, 90]. The effect of alcohol in SS warrants further studies.

VD deficiency has been associated with various ADs including multiple sclerosis, SLE, and RA among others

Table 3 Contrasting characteristics of SS and AITD

	AITD	SS	Ref
Target organ	Thyroid gland, thyrocytes	Salivary and lachrymal glands mainly, epithelial cells. Can affect any exocrine gland	[6, 7]
Immunopathogenic mechanism	Cell and antibody-mediated injury. Dysregulation of T-regs	Cell and antibody-mediated injury. Dysregulation of T-regs	[3, 6, 7, 9, 92]
Embryology	Endodermal origin Follicular cells: epithelial cells	Major salivary glands: ectodermal origin. Minor salivary glands: endodermal and ectodermal origin. Secretory cells: epithelial cells	[46, 47]
Epidemiology	Affects 2–5% of general population HT: prevalence 1/1.000 persons GD: 20–25/100.000	North America: 320/100.000 Europe: 200–3.000/1100.000	[9]
Sex ratio	HT: 18:1 GD: 10:1	9:1	[9]
Age at onset	All ages, mainly adults HT: 4th decade GD: 5th to 6th decade	4th to 6th decade	[18]
Polyautoimmunity	34% SSc, RA, SLE, MS, SS	10–52% AITD mainly HT, RA, SLE, AIH, PBC, SSc	[4, 9, 37]
Genetics	Polygenic HLA and non-HLA genes (Fig. 2)	Polygenic HLA and non-HLA genes (Fig. 2)	[14, 53, 54, 63, 68, 69, 71–73, 76]
Autoimmune ecology	Cigarette smoking has been described as a risk factor for GD but seems to be protective for the development of HT. Viral and bacterial infections have been associated with both GD and HT. Low-to-moderate alcohol consumption is associated with a lower risk of HT and GD. Evidence of the role of VD in AITD is controversial. The effect of coffee and exposure to other environmental toxics warrants further studies.	Cigarette smoking has showed controversial results. Several viral infections have been associated with SS. The effect of alcohol on SS warrants further studies. Evidence of the role of VD is not unanimous. The effect of coffee and exposure to other environmental toxics warrants further studies.	[73, 79–83, 91]
Main clinical manifestations	HT: depression, sleepiness, slow discourse, goiter, bradycardia, constipation, weight gain, oligomenorrhea, myalgias, arthritis, xerosis, cold intolerance GD: tremor, insomnia, hyperreflexia, ophthalmopathy, goiter, tachychardia, diarrhea, weight loss, irregular menses, fatigue, muscular weakness, heat intolerance, diaphoresis	Xerophthalmia, xerostomia, xerosis, xerotrachea, gastritis, constipation, dyspareunia, fatigue, polyarthralgia, myalgia. Organ specific compromise: lung, cardiovascular, gastrointestinal, renal, neurological and hematological involvement	[9]
Autoantibodies	HT: anti-TPO >90%, anti-Tg 50–90%, TRAb (blocking) 10%, NIS 20%, pendrin 11% GD: anti-TPO 40–70%, anti-Tg 20–40%, TrAb (stimulating) 90%, NIS 11%, pendrin 74%	Anti-Ro/SSA 33–74%, anti-La/SSB 23–52%, RF 36–74%, ANA 59–85%, cryoglobulins 9–15%, ACPA 3–10%, AMA 1.7–13%, ACA 3.7–27%, anti-M3 receptors 62.2–81.1%, anti-CA 12.5–20.8%, ASMA 30–62%	[9]
Treatment	HT: thyroid hormone replacement therapy GD: thyroid hormone replacement therapy after anti-thyroid medication, radioactive iodine therapy, or surgery.	Symptomatic, immunosuppression, biological therapy	[9]

AITD, autoimmune thyroid disease; *SS*, Sjögren's disease; *HT*, Hashimoto's thyroiditis; *GD*, Graves' disease; *SSc*, systemic sclerosis; *RA*, rheumatoid arthritis; *SLE*, systemic lupus erythematosus; *MS*, multiple sclerosis; *AIH*, autoimmune hepatitis; *PBC*, primary biliary cholangitis; *VD*, vitamin D; *Anti-Ro/SSA*: anti-Ro antibodies; *anti-La/SSB*, anti-La antibodies; *RF*, rheumatoid factor; *ANA*, anti-nuclear antibodies; *ACPA*, anti-citrullinated peptide antibody; *AMA*, anti-mitochondrial antibodies; *ACA*, anti-centromere antibodies; *Anti-M3 receptors*, anti-muscarinic receptor antibodies; *Anti-CA*, anti-carbonic anhydrase antibodies; *ASMA*, anti-smooth muscle antibodies; *anti-TPO*, thyroperoxidase antibodies; *anti-Tg*, thyroglobulin antibodies; *TRAb*, TSH receptor antibodies; *NIS*, sodium/iodine symporter

[79]. However, no consensus exists regarding the effect of low levels of VD on SS [91]. Just as in the case of SS, evidence of the effect of VD on AITD is controversial [73]. However, it seems that low VD levels may be a risk factor for developing AITD [79].

Conclusions

Overt thyroid polyautoimmunity, in particular HT, is frequent in SS patients. The general characteristics of SS and HT as well as genetic and environmental issues are summarized in Fig. 1 and Table 3 [3, 4, 7, 9, 14, 18, 37, 46, 47, 53, 54, 63, 68, 69, 71–73, 76, 79–83, 91, 92]. Although the clinical expression of SS varies slightly when HT coexists, further studies intended to evaluate the influence of genetic and environmental factors on polyautoimmunity are warranted. Last, patients with latent thyroid polyautoimmunity, which corresponds to the presence of thyroid autoantibodies in euthyroid patients with no goiter, may progress to overt thyroid disease [93, 94]; thus, long-term follow-up of them is necessary.

We acknowledge the shortcomings of this retrospective study, including sample size, confounding (other associated factors may be present that were not measured), and missing data. Our study could not determine causation, only association. Nevertheless, the results of this monocentric study where patients were unselected (i.e., this is the "real world") add further evidence about the coexistence of SS and HT and are encouraging. Spite of limitations, results and review of literature about similarities and differences between SS and AITD allow us to conclude that SS and AITD share common physiopathological mechanisms as part of the autoimmune tautology; however, they are nosologically different. Therefore, their coexistence should be interpreted as polyautoimmunity and not as the same disease nor as "secondary" disease.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Ethical Approval This study was done in compliance with Act 008430/1993 of the Ministry of Health of the Republic of Colombia, which classified it as minimal-risk research. All patients voluntarily agreed to participate in the study as indicated by their reading and signing the informed consent. The institutional review board of the Universidad del Rosario approved the study design.

Informed Consent Informed consent was obtained from all individual participants included in the study as part of the project "Common Mechanisms of Autoimmune Diseases."

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