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Review

Systemic sclerosis at the crossroad of polyautoimmunity

Muriel Elhai [a,b], Jerôme Avouac [a,b], André Kahan [a], Yannick Allanore [a,b,*]

[a] Rheumatology A Dpt, Paris Descartes University, Sorbonne Paris Cite, Cochin Hospital, APHP, 27 rue du Faubourg Saint-Jacques, 75014 Paris, France
[b] INSERM U1016, UMR 8104, Institut Cochin, University Sorbonne Paris Cité, 75014 Paris, France

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ABSTRACT

Objectives: Several epidemiological studies have revealed the co-occurrence of other autoimmune diseases (AIDs) within patients with systemic sclerosis (SSc). However, some of these studies were based on small cohorts and wide ranges of prevalence have been reported. Therefore to overcome these limitations of individual studies, we sought to perform a meta-analysis to determine the accurate prevalence of polyautoimmunity in SSc.
Methods: We performed a systematic review and a meta-analysis of literature in MEDLINE and Embase databases from January 1960 to March 2013. All cohort studies reporting on prevalence of other AIDs known to be associated with SSc were analyzed. Prevalence of polyautoimmunity and of each AID were then calculated.
Results: Ten studies reporting polyautoimmunity were identified corresponding to a total of 6102 SSc patients. Overall 1432 patients with at least one AID were identified corresponding to a weighted prevalence of polyautoimmunity equal to 25.7% CI 95% [20.1%–31.6%]. Overall 208/5139 SSc-patients had at least two additional AIDs resulting in a weighted prevalence of 3.9% [3.3%–4.4%]. The most prevalent associated AIDs were autoimmune thyroid disease (10.4%) followed by Sjögren's syndrome (7.7%) and dermatopolymyositis/polymyositis (5.6%).
Conclusion: Our results confirm that SSc polyautoimmunity is a frequent condition in SSc affecting a quarter of SSc-patients. The impact on the phenotype and also on the management and therapy will need to be addressed now in further works.

Contents

* Corresponding author at: Service de Rhumatologie A, Hôpital Cochin 27 rue du Faubourg Saint-Jacques, 75014 Paris, France. Tel.: +33 1 58 41 25 63; fax: +33 1 58 41 26 24.
E-mail address: yannick.allanore@cch.aphp.fr (Y. Allanore).

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1. Introduction

Systemic sclerosis (SSc) is a complex incurable multiorgan disease affecting the immune system, the microvascular network and the connective tissue [1,2]. SSc is characterized by a fibrotic phenotype resulting from the accumulation of extracellular matrix components, mainly collagens [3]. Its pathogenesis remains partially unknown, but it is believed that both genetic and environmental factors contribute to disease susceptibility and clinical expression [4]. Autoimmunity plays a pivotal role in SSc-pathogenesis; anti-nuclear antibodies are detected in up to 90% of SSc-patients and correspond to multiple SSc-specific auto-antibodies [1,5,6]. Both genetic and epidemiologic studies have suggested that SSc shares a genetic background with other autoimmune diseases (AIDs) [4,7–30]. Genetic studies have highlighted some susceptibility genes predisposing to multiple AIDs [4,7,31]. And we recently reported that some variant, such as a regulatory one located in TNFAIP3 region, was associated for SSc polyautoimmunity (i.e. AIDs co-occurring within patients) [32].

Epidemiological studies have revealed the existence of both polyautoimmunity and familial autoimmunity in SSc-patients (i.e. co-occurrence of AIDs in their families) [8,10–30]. According to studies, several AIDs were frequently associated with SSc in more than 10% of patients [8,10,12,15–18,20–22]. However, prevalence of polyautoimmunity and of each AIDs were highly variable from study to study [8,10–30]. Therefore, the precise frequencies of polyautoimmunity in SSc and of each AID associated with SSc remain unclear. Disparities across studies may be caused by small sample sizes and selection bias resulting in low statistical power and cohort's heterogeneity. Therefore to overcome the limitations of individual studies, increase statistical power thanks to a large cohort and resolve inconsistencies, we decided to perform a meta-analysis to determine the accurate prevalence of polyautoimmunity and of each AID known to be associated with SSc.

2. Materials and methods

2.1. Inclusion of the studies

The meta-analyses of observational studies in epidemiology (MOOSE) guidelines were followed [33]. For prevalence of polyautoimmunity in SSc, we searched MEDLINE and Embase databases between January 1960 and March 2013 using the terms (scleroderma or systemic sclerosis) [MesH] AND (autoimmunity). Eligible studies were cohort studies with SSc diagnosed according to ACR criteria [34] or Leroy's criteria [35] and reporting at least the prevalence within the cohort of two AIDs known to be associated with SSc (i.e. Sjögren's syndrome (SjS), dermatomyositis/polymyositis (DM/PM), rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), autoimmune thyroid disease (AITD) and primary biliary cirrhosis (PBC)). Secondary SjS was defined by the revised American-European consensus classification criteria or the 1999 Japanese Ministry of Health and Welfare's diagnostic criteria for SjS [36]. SLE and RA were defined by the revised classification criteria from the American College of Rheumatology [37,38]. PM and DM were diagnosed using the Bohan and Peter criteria [39]. PBC was diagnosed by combining laboratory, immunological and/or histological data or on criteria used in Japan [40–43]. AITD was diagnosed according to clinical and biological criteria including thyroid hormone levels and the detection of antithyroid antibodies [44]. We also investigated the prevalence of each AID using the terms (scleroderma or systemic sclerosis) [MesH] AND (Sjögren's syndrome)/(systemic lupus erythematosus)/(rheumatoid arthritis)/(dermatomyositis)/(polymyositis)/(autoimmune thyroid disease)/(primary biliary cirrhosis) [MesH], respectively. Multi autoimmune syndrome was defined by the presence of two or more other AIDs in a single SSc-patient [45]. Other SSc-cohort studies as well as reference lists of the papers initially detected were also searched by hand to identify additional relevant reports. In order to identify recent studies not yet published, we also searched in European League against Rheumatism (EULAR)/ACR congress abstract archives of 2011 and 2012. No language restriction was applied. Studies were excluded if they only referred to antibody prevalence.

2.2. Data extraction

From each study, we extracted data including localization of the study, period of follow-up, total number of SSc-patients, total number of SSc-patients affected by polyautoimmunity and by each of the AIDs investigated as well as clinical phenotype and antibodies prevalence, when available. The mid-cohort was calculated as the median year between the starting year of inclusion period and the ending year of the follow-up period.

2.3. Statistical analysis

All data analysis was performed using MedCalc® version 9.2.1.0. Data were presented as mean ± standard deviation (SD) for continuous variables and numbers (percentages) for categorical variables. Data were statistically analyzed using chi-square tests for differences in frequency between 2 normally distributed continuous variables. A p value < 0.05 was considered statistically significant. Prevalence of polyautoimmunity was calculated using data of studies assessing at least 2 AIDs known to be associated with SSc. The prevalence was calculated by dividing the number of patients with polyautoimmunity (or the specific AID investigated) by the number of patients studied. We then used the Freeman–Tukey transformation for each prevalence. This is a variance stabilizing transformation that removes the dependence of the variance on the mean of the transformed proportion (i.e., it corrects for overdispersion). We then calculated the pooled estimate for all studies (with 95% confidence interval (CI 95%)), which was backtransformed afterward using the DerSimonian and Laird method. This method is used for fitting the random effects model for meta-analysis to incorporate heterogeneity. With the prevalences calculated, aggregation for different AIDs was calculated by dividing the prevalence of a given AID in SSc-patients by the prevalence in the general population (λ). We extracted data on prevalences from one meta-analysis, which determined worldwide prevalences of AIDs [46]. Correlations were assessed using Spearman rank correlation coefficient (rho).

3. Results

The search retrieved 5738 articles. Overall, 5683 were excluded on the basis of their title or abstract resulting in 55 articles being examined for the full text (Fig. 1). Overall 22 studies responded to inclusion criteria and were included in the present analysis (Table 1) [8,10–30].

3.1. Prevalence of polyautoimmunity

Ten studies reporting several AIDs known to be associated with SSc were identified [8,10,12,15–18,20–22]. These studies provided a total sample of 6102 patients (women 87.1%, 35% of diffuse cutaneous subtype). Mean age at assessment was 57.6 (±3.1) years whereas mean disease duration was 10.6 (±2.3) years. Mean age at diagnosis was 47.6 (±2.6) years. Anti-Scl 70 antibodies were detected in 726/3145 (23.1%) SSc-patients and anticentromere antibodies were present in 1130/3143 (35.9%) patients. Four studies investigated anti-U1-RNP antibody positivity in their SSc-cohort and detected it in 216/2874 (7.5%) cases. The period of follow-up ranged from 1973 to 2011. Mid-cohort was comprised between 1987 and 2011, with 2 studies before 2000 ($n = 779$ patients) and 8 after ($n = 5323$ patients).

Polyautoimmunity was found more frequently in European patients (852/3603 (23.6%)) than in North American patients (325/1639 (19.8%), $p < 0.05$%).

Prevalence of polyautoimmunity varied across studies from 10.9% to 43.9%. It was equal to 20.3% in studies before 2000 and to 23.9% in

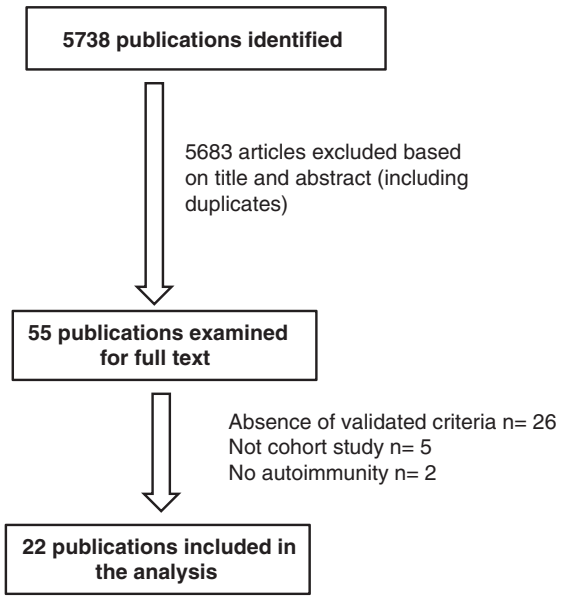

Fig. 1. Study flow chart.

those after 2000 ($p = 0.03$). Polyautoimmunity did not correlate with age at assessment (rho = 0.48; $p = 0.13$) or age at diagnosis (rho = 0.07; $p = 0.85$). However, another AID was more frequently detected in SSc-patients older than 48 years at diagnosis (27.1%) than those younger (21.1%) ($p < 0.01$).

Overall 1432 patients with at least one AID were identified corresponding to a weighted prevalence of polyautoimmunity equal to 25.7% CI 95% [20.1%–31.6%] (Fig. 2). Eight studies also reported the number of patients with multi autoimmune syndrome [8,10,16–18,20–22]. Overall 208/5139 SSc-patients had at least two other AIDs resulting in a weighted prevalence of 3.9% [3.3%–4.4%].

3.2. Phenotype of patients with polyautoimmunity

Only six studies provided information regarding the phenotype of SSc-overlap patients [8,10,15,17,18,22]. Patients with polyautoimmunity were more frequently women (607/654 (92.8%) vs. 1524/1755 (86.8%); $p < 0.01$) and of limited cutaneous subtype (314/385 (81.6%) vs. 925/1439 (64.3%); $p < 0.01$).

3.3. Prevalence of each autoimmune disease and phenotype analysis

3.3.1. Prevalence and phenotype of patients with systemic sclerosis and Sjögren syndrome

Eleven studies reported prevalence of SjS in SSc-patients. Prevalence of SjS in the cohorts ranged from 0% to 33.9% [8,10,12,15–18,20–22,29]. Overall 513/6220 SSc had also SjS, with a weighted prevalence of 7.7% [4.5%–11.6%] (Fig. 3A). SSc-patients with SjS were preferentially of limited cutaneous subtype (195/245 (79.6%) vs. 1107/1615 (68.5%), $p < 0.01$) [10,15,17,29].

3.3.2. Prevalence of patients with systemic sclerosis and autoimmune thyroid disease

Prevalence of AITD was reported by 7 studies [8,10,11,19–22]. Prevalence of AITD varied from study to study from 1.4% to 23.1% with a total of 300/2816 patients with AITD. This corresponded to a weighted prevalence of 10.4% [6.1%–15.5%] (Fig. 3B).

3.3.3. Prevalence and phenotype of patients with systemic sclerosis and primary biliary cirrhosis

PBC was investigated in 11 studies. PBC was detected in 157 patients/5024 with a weighted prevalence equal to 3.0% [1.7%–4.6%] [range: 0–15.6%] [8,10,13,14,17,20–25] (Fig. 3C).

SSc-patients with PBC were more frequently women (78/82 (95.1%) vs. 1822/2092 (87.1%), $p < 0.05$), of limited cutaneous subtype (104/119 (87.4%) vs. 2045/3201 (63.9%), $p < 0.01$) and with anticentromere antibody positivity (78/96 (81.3%) vs. 873/2517 (34.7%), $p < 0.01$) [10,13,14,23–25].

Table 1
Main characteristics of the studies included.

Study	Localization	Study period	Number of patients	Age, years [a]	Age, years [b]	Female n (%)	Disease duration, years	Dc SSc n (%)	ACA n (%)	Anti-Scl70 n (%)
Koumakis E [21]	France	2010–2011	373	61.1		327 (88%)		204 (55%)		
Hudson M [12]	Canada	2004–2011	963	54.25		833 (87%)	11.04	356 (38%)	334/961 (35%)	150 (16%)
Simic-Pasalic K [22]	Serbia		153	59.1		138 (89%)	9.2	67 (44%)	61 (40%)	75 (49%)
Imura-Kumada S [25]	Japan		225	53.4		192 (85%)	6.5	119 (53%)	110 (49%)	27 (12%)
Hashimoto A [15]	Japan	1973–2008	405		51	376 (93%)	14	135 (33%)	128 (36%)	84 (24%)
Pakozdi A [16]	UK	1999–2007	1700					564 (33%)		
Balbir-Gurman A [17]	Israel	2004–2009	165					42 (25%)		
Ueda-Hayakawa I [26]	Japan		146			128 (88%)		60 (41%)	60 (41%)	38 (26%)
Cavazzana I [14]	Italy	1983–2010	201			172/198 (87%)		67/198 (34%)	65/197 (33%)	63/195 (32%)
Simeon-Aznar CP [13]	Spain	2006–2008	916		51.2	801 (87%)	6.2		356 (39%)	173 (19%)
Avouac J [10]	France		585	57		498 (85%)	11	191 (33%)	193 (33%)	149 (25%)
Avouac J [10]	Italy		547	63		491 (90%)	13	136 (25%)	276 (50%)	136 (24%)
Assassi S [23]	USA	2001–2007	817	53.95		725 (89%)	9.16	326 (40%)	246 (30%)	156 (19%)
Hudson M [8]	Canada	2004–2007	429	55		369 (86%)	11	197 (46%)		
Hudson M [8]	Colombia	2004–2007	290	54		264 (91%)	7	61 (21%)		
Meyer O [18]	France	1975–2002	127		48.4	105 (83%)		24 (19%)	23 (18%)	45 (35%)
Meyer O [18]	USA	1986–88	247		47.6	183 (91%)		116 (47%)	52 (21%)	54 (22%)
Antonelli A [11]	Italy	1999–2004	202	55		184 (91%)	12.9	32 (16%)	71 (35%)	79 (39%)
Caramaschi P [20]	Italy		118	57.2	48.5	106 (90%)	8.7	40 (34%)	63 (53%)	33 (28%)
Szücs G [27]	Hungary		477							
Biro E [19]	Hungary		119							
Jinnin M [28]	Japan	1990–2001	173			158 (91%)	8	63 (36%)	51 (30%)	57 (33%)
Jacobsen S [24]	Denmark	1980–1993	230	58		189 (82%)	11		79 (34%)	31 (13%)
Kobak S [29]	Turkey		118	48.3		108 (92%)	8.2	58 (49%)	53 (45%)	58 (49%)
Marrone M [30]	Italy	2004–2005	60	50.1		57 (95%)	7.5	8 (13%)	14 (23%)	34 (57%)

N: number, Dc: diffuse cutaneous subtype, SSc: systemic sclerosis, ACA: anticentromere antibodies.
[a] Age at assessment.
[b] Age at diagnosis.

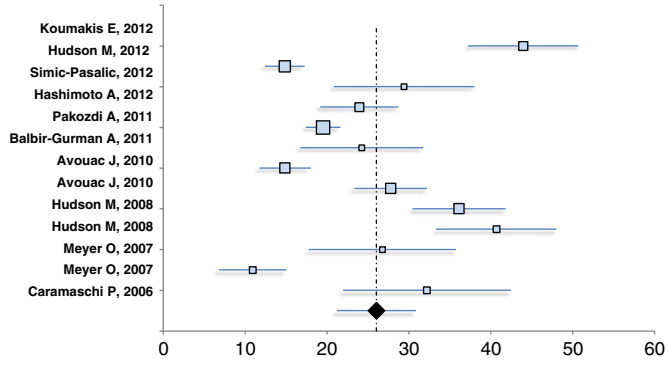

Fig. 2. Forest plot of polyautoimmunity for patients with systemic sclerosis. Each square represents an individual prevalence estimate, the size of the square being proportional to the weight given to the study. The lines represent the 95% CI for the point estimate in each study. The diamond represents the combined prevalence.

3.3.4. Prevalence and phenotype of patients with systemic sclerosis and rheumatoid arthritis

Fourteen studies investigated frequency of RA in their cohorts [8,10,12,15–18,20–22,26–28,30]. They found frequencies between 0% and 17.5% with 345 cases of RA among 6958 SSc-patients. The weighted prevalence of RA was calculated at 4.2% [1.7%–7.2%] (Fig. 3D).

Patients with concomitant RA were of limited cutaneous subtype in 34/49 cases (69.4%) vs. 497/735 (67.6%) patients without RA ($p = 0.92$) [15,26,28,30].

3.3.5. Prevalence and phenotype of SSc-patients with dermatomyositis/polymyositis

Seven reports investigated PM/DM associated with SSc with 256 cases/4605 patients studied [10,12,16–18,20,22]. Frequencies were between 1.7% and 15.7% resulting in a weighted frequency of 5.6% [3.7%–7.8%]. SSc-patients with DM/PM were of limited cutaneous subtype in 65.3% of the cases (49/75) and those without DM/PM in 71.5% (1163/1627) ($p = 0.30$) [10,15,17].

3.3.6. Prevalence of patients with systemic sclerosis and systemic lupus erythematosus

SLE was detected in 127/5383 patients with a weighted prevalence of 2.6% [1.6%–3.9%] [range: 0.5%–7%] [10,12,15–18,20–22].

3.4. Aggregation of autoimmune diseases in systemic sclerosis

Recurrence risk values λ were calculated to approximately 1120 for DM/PM, 750 for PBC, 108 for SLE, 26 for SjS, 5 for AITD and 4 for RA [46].

4. Discussion

So far, results concerning prevalence of polyautommunity in SSc have remained conflicting varying from 10.9% to 43.9% [8,10,12,15–18,20–22]. Similarly, the prevalence of each AID in SSc is unknown [8,10–30]. To our knowledge, our study is the first one to investigate the worldwide prevalence of polyautoimmunity in SSc in a meta-analysis. With this method, we can conclude that concurrent AIDs are common in SSc-patients with

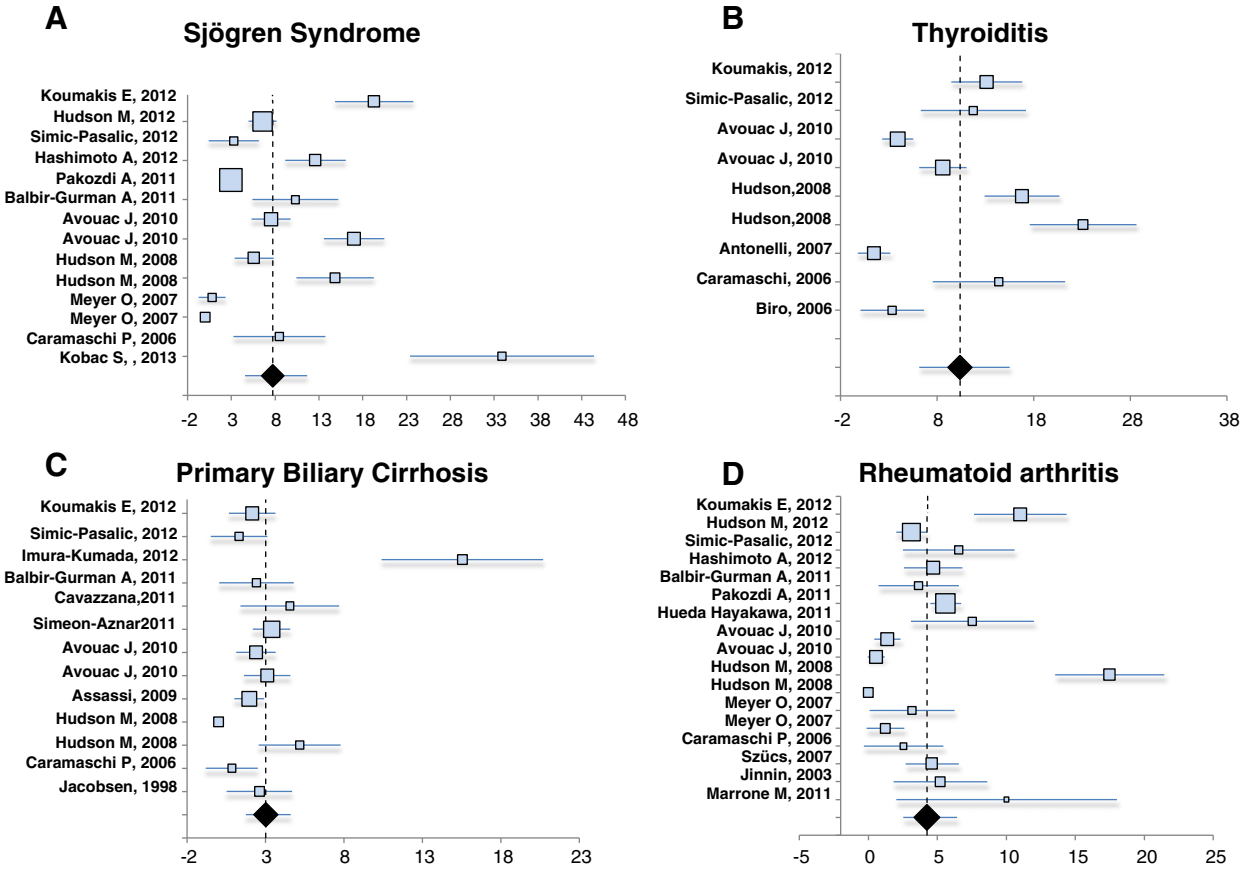

Fig. 3. Forest plots of prevalence of Sjögren syndrome (A), autoimmune thyroiditis (B), primary biliary cirrhosis (C) and rheumatoid arthritis (D) in patients with systemic sclerosis according to studies. Each square represents an individual prevalence estimate, the size of the square being proportional to the weight given to the study. The lines represent the 95% CI for the point estimate in each study. The diamond represents the combined prevalence.

a prevalence of 26%. The most prevalent associated AIDs are AITD (10.4%) followed by SjS (7.7%) and DM/PM (5.6%).

Several reasons may account for the heterogeneity in studies and as a result in our meta-analysis: small size (median number of patients in a cohort: 373), geographical differences, differences in population characteristics (age and phenotype) and in study periods. For example, we found a higher prevalence of polyautoimmunity in SSc in recent studies as compared to the older ones. This result probably reflects a bias of underdiagnoses in older studies. Thus some AIDs were not searched for in cohorts studied before 2000, such as PBC or DM/PM [15,18]. We can hypothesize that with increasing knowledge in the spectrum of AIDs associated with SSc (and polyautoimmunity), the prevalence of polyautoimmunity will be found increased in further studies.

Our results confirm that prevalence of polyautoimmunity is much higher in SSc-patients (26%) than reported in the general population (3–8%) [46]. Consistent with this result, our aggregation analyses disclosed an aggregation of AIDs in SSc with values over 1 for all AIDs investigated. Interestingly, this analysis revealed extreme values with individual recurrence risk values over 700 for some diseases, such as PBC and DM/PM.

Our results are also supported by studies in other AIDs, such as PBC and SjS, which demonstrated with the opposite approach an association with SSc more frequent than might be expected in the general population [47–49].

The concept of "shared autoimmunity" is strengthened by the familial aggregation of AIDs, detected in 1/3 of SSc-relatives [8,21], and by the existence of polyautoimmunity in patients affected by these SSc-associated AIDs, such as AITD, SLE, PBC and SjS [4,7,9,47–52]. Furthermore, some data suggest common pathogenic mechanisms in some of these AIDs [53]. Altogether, these results are concordant with genetic studies, revealing some degree of common genetic susceptibility. This has been known for a long time by the associations of certain Human Leukocyte Antigen (HLA) loci with different AIDs. And this has been confirmed by recent studies identifying non-HLA common susceptibility genes involved in diverse immune pathways [4,7,31]. This supported the autoimmune tautology indicating that different AIDs with a wide heterogeneity in their phenotype might represent pleiotropic outcomes of non-specific disease genes [54]. However, the mechanisms involved in the development of the final clinical phenotype are unknown. Therefore, understanding the relationship of genotype to phenotype is an extremely important goal for research. The study of specific environmental triggers and their putative interaction with susceptibility genes should be helpful in further studies to better understand the development of each specific phenotype [55,56].

Similarly, the mechanism involved in the development of multiple AIDs in one individual and the effect of this polyautoimmunity on the final clinical autoimmune phenotype are not well understood. Our results suggest that polyautoimmunity in SSc could influence both disease phenotype and severity. Patients with polyautoimmunity seem to have a milder disease (higher frequencies of women, of limited cutaneous subtype and of anticentromere positivity). This is concordant with previous reports in SSc [4,10,13,14,23–26]. Similarly in PBC, patients with an overlap SSc-PBC seem to have a milder disease [57]. We can hypothesize that some immunological interactions in the presence of an additional AID may favor a better outcome of the disease. Therefore, further studies are needed to better determine the effect of an additional AID on SSc-phenotype.

Our study should be interpreted within its limitations. First, this meta-analysis might be limited by the heterogeneity across the studies included. However, we considered this variability in our analysis and reduced it using the DerSimonian and Laird method. Furthermore, some limitations related to cohort studies may bias our results. Ethnicity, demographical characteristics, clinical subsets and organ involvement may differ across studies. Unfortunately, we could not stratify our results according to ethnicity because of missing data in studies included. However, we observed that North American patients were less affected by polyautoimmunity than European. Height percent of the patients with available data had anti-RNP antibodies, underlying the question of a misdiagnosis between mixed connective tissue disease and SSc with polyautoimmunity [58]. However, to reduce this bias, inclusion criteria were international validated criteria for SSc and also for the other AIDs. These rigorous criteria lead to exclusion of studies reporting sicca syndrome (and not SjS) and those with diagnosis of PM/DM in cases of myositis related to SSc. Moreover, we did not assess other AIDs, such as diabetes, multiple sclerosis, vitiligo, autoimmune hepatitis …. Indeed, the prevalence of these AIDs was assessed in a minority of the studies included. Finally we cannot exclude a bias of underdiagnoses in some of the studies included, depending on the screening method used and its repetition or not during the disease course. This underlines the need of large contemporary cohorts, with prospective and repeated standardized data collection, to better study the prevalence of associated AIDs in SSc. Thus, the EULAR Scleroderma Trial and Research (EUSTAR) group database, enabled by the major efforts of multiple medical centers, should allow studying prevalence of AIDs associated with SSc, phenotype of the SSc-patients with polyautoimmunity and the chronology of appearance of the different diseases in a large population of SSc-patients.

In conclusion, polyautoimmunity is a common condition in SSc, affecting one quarter of the patients. The most frequent associated AIDs are AITD, SjS, DM/PM and RA. Further studies are warranted to increase our knowledge about the common mechanisms of autoimmunity and the effect of polyautoimmunity on SSc-phenotype leading to potential new approaches for management and treatment of SSc-patients with polyautoimmunity.

Take-home messages

- Polyautoimmunity affects one quarter of the systemic sclerosis-patients.
- The main overlapping disorders are autoimmune thyroiditis and Sjögren syndrome.
- Systemic sclerosis-patients with polyautoimmunity seem to have a milder disease.

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