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Thyroid disorders in patients with systemic sclerosis: A systematic review and meta-analysis

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Systemic sclerosis (SSc) is one common autoimmune disease characterized by multi-organ fibrosis, vascular abnormalities, and immune disorders [1]. The incidence and prevalence of SSc have been increasing for the past decades [2]. Patients with SSc are at higher risk of depression and their health-related quality of life suffer dramatically for the manifestations, such as skin thickening, pulmonary fibrosis and hypertension, joint contractures, chronic diarrhea, and renal failure [3]. Autoimmune thyroid disease (AITD) and thyroid dysfunction are both common thyroid disorders. AITD, one of the immune-mediated diseases, mainly includes Graves' disease (GD) and Hashimoto's thyroiditis (HT) [4]. GD mainly results from the abnormal increase of thyroid-stimulating antibodies, while HT is characterized by high concentrations of thyroid autoantibodies against thyroid peroxidase (TPOAb) and thyroglobulin (TgAb). Several studies have investigated the association of thyroid disorders and SSc, but the results of them vary substantially and thus the relationship between them is still controversial. Moreover, the small sample size of them restricted their power to determine a precise prevalence of thyroid disorders in SSc and draw a safe conclusion about the association between them. Therefore, we performed this meta-analysis to get a more precise estimation on the prevalence of thyroid disorders in SSc and the relationship between thyroid disorders and SSc.

We searched Pubmed, Embase, and Web of Science for eligible studies investigating the relationship between thyroid disorders and SSc. The literature search was from inception to September 16, 2018. No language restriction was applied. Studies were included in the meta-analysis if they met the following inclusion criteria: (1) Cross-sectional, cohort or case-control studies; (2) the prevalence of thyroid disorders in patients with SSc, or the association between thyroid dysfunction and SSc was reported; (3) Sufficient data, such as risk ratio (RR) and odds ratio (OR), were provided to calculate the prevalence or risk estimates of thyroid disorders in SSc patients. Two authors independently extracted data from each study. We evaluated the quality of the studies by use of Newcastle-Ottawa Scale (NOS). We conducted all statistical analyses using the R3.2.3 and Stata (Version 12.0). Considering the obvious difference among those included studies, we used random-effects model to combine prevalence or ORs. Subgroup analysis was also performed by the types of AITD or thyroidal dysfunction. A P value $< .05$ was reckoned statistical significance.

A total of 46 studies were finally included into the meta-analysis (Supplementary fig. 1). The characteristics of the included studies were summarized in Supplementary table 1. The summary prevalence of AITD in SSc patients was 19.7% (95% CI 12.0%– 30.6%) (Table 1; Supplementary fig. 2). What's more, as shown in Table 1, the prevalence of TPOAb positivity was highest in patients with SSc (25.2%, 95%CI 19.9%–31.5%) (Table 1; Supplementary fig. 3), followed by HT (22.7%, 95% CI: 17.5%–28.9%) (Table 1), TGAb positivity (20.6%) (Table 1; Supplementary fig. 3), and GD (1.5%, 95% CI: 08%–3%) (Table 1). The pooled prevalence of thyroid dysfunction in SSc patients was 19.5% (95%CI 16.5%–22.9%) (Table 1; Supplementary fig. 2). Specifically, the prevalence of hypothyroidism in SSc patients was highest (18.3%, 95%CI 14.4%–22.8%), followed by subclinical hypothyroidism (12.3%, 95%CI 8.1%–18.3%), overt hypothyrodism (4.9%, 95%CI 2.8%–8.3%), hyperthyroidism (4%, 95%CI 3.0%–5.4%), subclinical hyperthyroidism (3%, 95%CI 1.9%–4.7%), and overt hyperthyroidism (1.7%, 95%CI 0.9%–3.1%) (Table 1).

As shown in Fig. 1, SSc was significantly associated with increased risk of AITD (OR = 3.42; 95%CI 2.56–4.56, $P < .001$) and HT (OR = 3.40; 95%CI 1.67–6.91, $P = .001$) (Fig. 1). Subgroup analysis also suggested that SSc significantly increased the risk of TPOAb positivity (OR = 3.01; 95%CI 2.04–4.45, $P < .001$), TGAb positivity (OR = 1.82; 95%CI 1.07–3.12, $P = .029$) and hypothyroidism (OR = 3.74; 95%CI 2.45–5.71, $P < 0.001$) (Fig. 1). However, meta-analysis of 4 studies indicated that hyperthyroidism was not associated with SSc ($P > .05$). No risk of publication bias in the meta-analysis on TPOAb, TGAb and hypothyroidism (all P Egger's test > 0.05).

Discussion

The study is the first meta-analysis assessing the prevalence of thyroid disorders in SSc patients and the association of thyroid disorders with SSc comprehensively. Our findings indicate that there is a remarkably high prevalence of thyroid disorders in patients with SSc and SSc is associated with increased risks of thyroid disorders.

Considering that thyroid autoimmune diseases and SSc might share same autoimmune elements, it is likely that these diseases could coexist in the same patient. To date, pathogenic mechanisms of this coexistence are not completely clarified. One study has revealed that genetics, environmental factors, immune defects and hormones may play crucial roles in polyautoimmunity [5]. For example, the prevalence of the Th1

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Table 1
Meta-analysis of the prevalence of thyroid disorders in SSc patients.

Analyses	No. of studies	Number	Events	I2	P value	Prevalence	95%CI
AITD	12	2878	516	96%	< 0.01	19.7%	12.0%–30.6%
GD	8	1316	14	34%	0.16	1.5%	0.8%–3.0%
HT	25	2821	628	90.1%	< 0.0001	22.7%	17.5%–28.9%
TGAb	17	1765	363	86%	< 0.01	20.6%	15.5%–26.8%
TPOAb	18	2274	538	88%	< 0.01	25.2%	19.9%–31.5%
Dysfunction	14	1483	289	51%	0.01	19.5%	16.5%–22.9%
Hyperthyrodism	7	1046	41	0%	0.89	4.0%	3.0%–5.4%
Subclincial hyperthyroidism	5	640	18	0%	0.72	3.0%	1.9%–4.7%
Overt hyperthyroidism	11	1566	19	39%	0.09	1.7%	0.9%–3.1%
Hypothyroidism	20	2514	479	85%	< 0.01	18.3%	14.4%–22.8%
Subclincial hypothyrodism	11	1172	149	84%	< 0.01	12.3%	8.1%–18.3%
Overt hypothyrodism	12	1614	84	81%	< 0.01	4.9%	2.8%–8.3%

AITD, autoimmune thyroid disease; GD, Graves' disease; HT, Hashimoto's thyroiditis; TgAb, thyroglobulin antibody; TPOAb, thyroid peroxidase antibody.

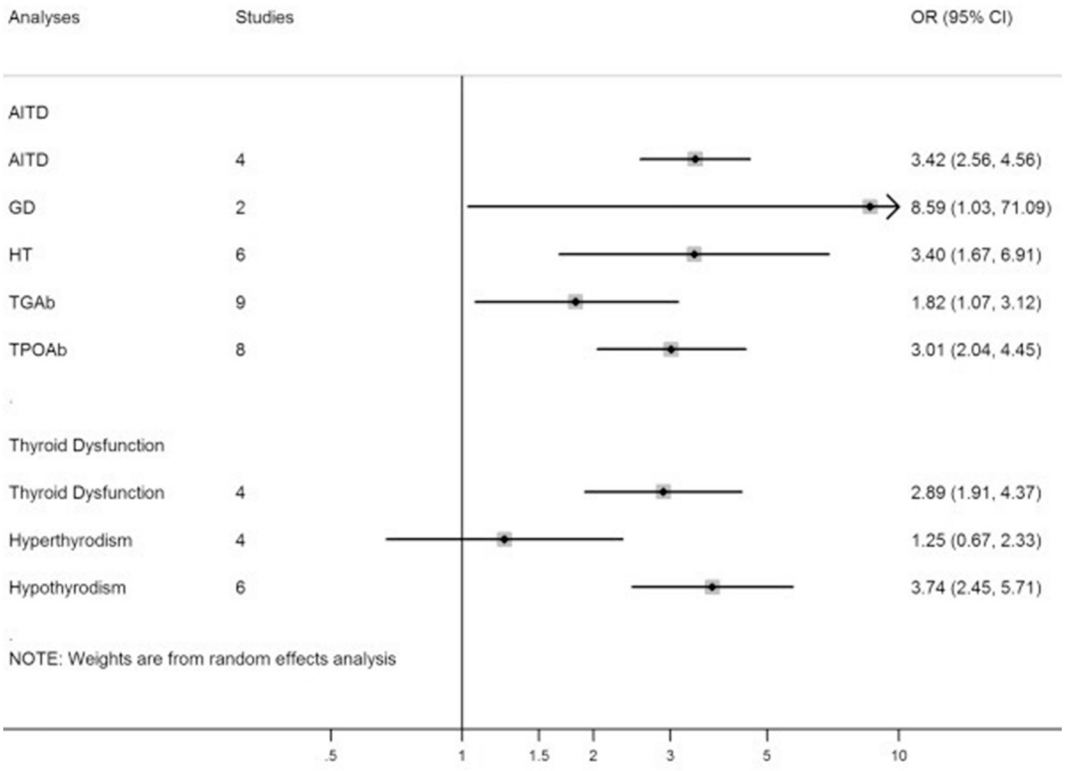

Fig. 1. Meta-analysis of association between thyroid disorders and SSc (AITD, autoimmune thyroid disease; GD, Graves' disease; HT, Hashimoto's thyroiditis; TgAb, thyroglobulin antibody; TPOAb, thyroid peroxidase antibody).

and Th2 immune reactivity in the both SSc and AITD might be one of the potential basis on which these diseases exist in the same subject [6].

The potential association of thyroid disorders with SSc deserves particular attention for its important application in the decision-making process of preventive, screening and therapeutic strategies of AITD in SSc patients, especially in female SSc patients. AITD may lead to subacute thyroiditis, myxedema coma and malignant lymphoma [7]. Indeed, it is clear that the presence of autoantibodies may be a risk factor for poor prognosis in autoimmune disease [8]. Evidence supported that thyroid antibodies could add to the risks of severe complications such as miscarriage, preeclampsia and preterm delivery in pregnancy associated with connective tissue diseases [9]. More importantly, thyroid dysfunction especially hypothyroidism has been associated with adverse obstetric outcomes, such as intrauterine growth restriction and low Apgar score [10]. Thus, it's strongly recommended that thyroid function and thyroid autoantibodies should be tested as a part of the clinical profile in patients with SSc, especially for female patients preparing for pregnancy.

Base on the evidence showed above, our meta-analysis conclude that patients with SSc are more likely to develop thyroid disorders than those healthy controls. Thus, routine tests about thyroid diseases, such as ultrasound, thyroid function and thyroid antibodies, are recommended to be included in the workup of patients with SSc. However, more prospective cohort studies are still needed to further strengthen the association of thyroid disorders and SSc.

Competing interests

The authors declare no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.autrev.2019.01.003.

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