

Thyroid Autoantibodies in Egyptian Patients with Autoimmune Rheumatic Diseases: Relation to Disease Activity and Functional Impairment

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ABSTRACT

Background: Autoantibodies against the thyroid seem to be more common in patients with rheumatic diseases than in the normal population. Their appearance may be linked to an associated autoimmune thyroid disease. Knowing the degree of association between rheumatic and thyroid diseases may help the clinician to make the correct decision.

Objectives: The aim of the work was to estimate the prevalence of thyroid autoantibodies among patients with systemic autoimmune rheumatic diseases with or without thyroid disorders and its association with disease activity and functional impairment.

Patients and Methods: The current study included 60 patients and 20 healthy controls. Patients were divided into three groups; systemic lupus erythematosus (SLE), rheumatoid arthritis (RA) and systemic sclerosis (SSc). Clinical and laboratory assessment were done to all patients including routine laboratory investigations and thyroid function tests (thyroid stimulating hormone [TSH], T3 and T4), and thyroid autoantibodies; anti-thyroglobulin (TgAb) and anti-thyroperoxidase (TPOAb).

Results: SLE group had significant ($P=0.018$) lower age than other groups. Antithyroid antibodies and thyroid disorders were more common in SSc and SLE patients than RA patients and control subjects; however, no significant difference between studied groups. Presence of autoantibodies with and without thyroid disorders was not associated with the activity or functional indexes evaluated.

Conclusion: The prevalence of thyroid autoantibodies in SLE and SSc patients was higher than in RA patients. No link could be established between the presence of thyroid autoantibodies and the results from any of the instruments used to measure inflammatory activity and functional impairment in these cases of rheumatic diseases.

Keywords: Thyroid autoantibodies, Autoimmunity, Rheumatic disease, RA, SLE, SSc

INTRODUCTION

Autoimmune thyroid disease (AITD) is a term used to describe a group of pathologies that has thyroid dysfunction, and an autoimmune response against this endocrine organ as its hallmark ⁽¹⁾. However, being a group of autoimmune diseases (ADs) clustered together, the clinical presentation varies among these diseases; it can be divided into those that cause hypothyroidism, hyperthyroidism, or both ⁽²⁾. The major antigens of thyroid autoantibodies are thyroglobulin (Tg), thyroid peroxidase (TPO) and thyroid-stimulating hormone receptor (TSH-R) ⁽³⁾. Hypothyroidism and rheumatic diseases share common clinical findings such as arthralgias, arthritis, myalgias, myopathy and fatigue, which need to be correctly diagnosed to be properly treated. Knowing the degree of association between rheumatic and thyroid diseases may help the clinician to make the correct decision ⁽⁴⁾.

Rheumatoid arthritis is a systemic disease characterized by inflammatory peripheral arthritis. An association between AITDs with or without

thyroid dysfunction and RA has been reported in adults; however, the pathogenic mechanism remains uncertain ⁽⁵⁾. SLE is an autoimmune disease that affects the skin, kidneys, musculoskeletal, hematologic systems, and it is characterized by the presence of various autoantibodies against self-components, especially double-stranded deoxyribonucleic acid and ribonucleic acid-binding nuclear proteins. Thyroid autoantibodies have been found more often in patients with SLE than in the general population and even in patients with no thyroid disease ⁽⁶⁾. Progressive systemic sclerosis (SSc) is a connective tissue disease, characterized by vascular abnormalities, multiorgan fibrosis and complex immune system alterations. The association of SSc with thyroid fibrosis, hypothyroidism and thyroid autoimmunity has been reported by several studies in a wide range of variability ⁽⁷⁾.

The aim of the current study was to estimate the prevalence of thyroid autoantibodies among patients with systemic rheumatic disease (SLE, RA and SSc) with or without thyroid



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disorders and its association with disease activity and functional impairment.

PATIENTS AND METHODS

This case control observational study included a total of sixty patients with rheumatic diseases and twenty healthy controls, recruited from Rheumatology Department and Out-patients' Clinic, Ain Shams University Hospital.

Ethical approval:

The study was approved by the **Ethical Committee of Ain Shams University** and written informed consent was obtained from subjects.

The included 60 rheumatic disease patients were divided into three groups; **Group 1** systemic lupus erythematosus; (SLE), **Group 2** rheumatoid arthritis; (RA) and **group 3** systemic sclerosis; (SSc), each consisted of 20 patients.

Clinical and laboratory assessment were done to all patients and controls including thyroid function tests (TSH, T3 and T4), and thyroid autoantibodies; anti-thyroglobulin (TgAb) and anti-thyroperoxidase (TPOab). SLE patients diagnosed by 2019 European League Against Rheumatism/American College of Rheumatology (EULAR/ACR) classification criteria for SLE which requires a positive ANA as obligatory entry criterion. Patients accumulating ≥ 10 points are classified as having lupus⁽⁸⁾. RA patients needed to have six points or more of the 2010 classification criteria from the ACR/EULAR⁽⁹⁾. SSc patients needed to achieve at least nine points in the 2013 ACR/EULAR classification criteria⁽⁷⁾.

Clinical evaluation was done including full history taking with emphasis on symptoms of disease activity, organ damage and medications. Disease activity assessment for SLE patients was performed using the SLE Disease Activity Index (SLEDAI)⁽¹⁰⁾ and damage assessment was done using the Systemic Lupus International Collaborating Clinics/American College of Rheumatology damage index (SLICC/ACR)⁽¹¹⁾. Disease activity assessment for RA patients was performed using the Disease Activity Score-28 using the erythrocyte sedimentation rate (DAS28-ESR)⁽¹²⁾ and the Health Assessment Questionnaire (HAQ) was done to quantify physical disability and the corresponding functional status⁽¹³⁾. For SSc patients; the Rodnan modified index (Rodnan-m) was measured to evaluate the degree of skin involvement⁽¹⁴⁾, and the Medsger index to evaluate the degree of systemic involvement⁽¹⁵⁾.

Routine Laboratory investigations were done including complete blood picture using coulter JS and cell counter, erythrocyte

sedimentation rate (ESR) by Westergren method, C-reactive protein with titer by immunoturbidimetric method, liver enzymes; aspartate aminotransferase (AST) and alanine aminotransferase (ALT), kidney function tests; creatinine and blood urea nitrogen (BUN) by calorimetric method and complete urine analysis. Protein/creatinine ratio in morning sample was estimated to evaluate proteinuria in SLE patients. Serum complement 3 and 4 were measured for SLE patients. Echocardiography, pulmonary function tests (PFT) and lung diffusion capacity (DLCO) for SSc patients. Thyroid profile; (TSH, T3 and T4), thyroid autoantibodies; anti-thyroglobulin antibody (TgAb) and anti-thyroperoxidase antibody (TPOAb) were done.

Statistical analysis

The collected data were coded, tabulated, and statistically analyzed using SPSS program (Statistical Package for Social Sciences) software version 23.0. Description of quantitative variables as mean, standard deviation (SD) and range. Description of qualitative variables as number (no) and percentage (%). Chi-square test was used to compare qualitative variables. One Way ANOVA test and Kruskal Wallis test were used instead of Chi-square test when one expected cell or more ≤ 5 . Independent t-test and Mann Whitney test were also used. Unpaired t-test was used to compare two independent groups as regard quantitative variables. P-value ≤ 0.05 was considered significant.

RESULTS

Sixty patients and 20 healthy controls were studied. The mean age for SLE patients was 34.25 ± 7.22 years (22–46), 18 patients were females. The median for SLEDAI was 9.00 (0–20), and SLICC/ACR-DI was 1 (0–3). Thyroid antibodies (TgAbs & TPO Abs) were positive in 5 (25%) SLE patients. The mean age for RA patients was 42.20 ± 9.63 years (26–66), all of them were females. The mean DAS score was 4.4 ± 1.19 (3.03–6.42). Thyroid antibodies were positive in 2 (10%) RA patients. The mean age for SSc patients was 40.60 ± 9.09 years (22–56), all of them were females. The mean Rodnan-m score was 13.2 ± 6.83 (4–26), and Medsger index mean score was 1.65 ± 0.67 (1–3). As regards PFTs in SSC, 4 patients (20%) had normal PFTs while 16 patients (80%) had restrictive PFTs. In SSc patients the mean DLCO was $78.10 \pm 7.89\%$ (65–90%) and the mean ejection fraction (EF) was $60.5 \pm 6.42\%$ (45–69%). Thyroid antibodies were positive in 6 (30%) SSc patients. The mean age for the control subjects was 35.80 ± 9.83 years (25–63), 12 patients were

females. Thyroid antibodies were positive in 3 (15%) subjects of the control group (Table 1). The prevalence of thyroid disorders (hypothyroidism and hyperthyroidism) in our study was (30%) in SLE patients, (5%) in RA patients, (25%) in SSC patients and (20%) in control group.

In the present study there was a significant difference (P=0.018) between studied groups as regard age; SLE group had lower age than other groups, high significant difference between studied groups as regard sex, while, no significant difference between studied groups as regard smoking (Table 2). There was no significant difference between studied groups as regard thyroid function tests (TSH, T3 and T4) (Table 3). There were more antithyroid antibodies (Tg Abs &

TPO Abs) in SSc and SLE groups; however, there was no significant difference between studied groups as regard ATA (Table 4). There was no significant difference (p=0.184) between studied groups as regard the presence or absence of thyroid diseases; however, they were more common in SSc and SLE patients (Table 5).

There was no significant difference between SLE patients with and without positive thyroid Abs as regard SLEDAI score and SLICC/ACR damage index (Table 6), the same was for SSc patients as regard Rodnan modified index and Medsger index (Table 7). Also, there was no significant difference between RA patients with and without positive thyroid Abs as regard DAS-28 ESR & HAQ scores (Table 8).

Table (1): Prevalence of thyroid diseases and antithyroid antibodies (ATA) in rheumatic disease patients & control group.

	RA group	SLE group	SSC group	Control group
Hypothyroidism	1	5	3	3
Hyperthyroidism	-	1	2	1
Anti Tg & Anti TPO	2	5	6	3
Anti Tg & Anti TPO with thyroid disease	0	1	1	0
Anti Tg & Anti TPO without thyroid disease	2	4	5	3

Table (2): Comparison between studied groups as regard demographic data.

		Control group	SLE group	RA group	SSC group	Test value	P-value	Sig.
		No. = 20	No. = 20	No. = 20	No. = 20			
Age (years)	Mean ± SD	35.80 ± 9.83	34.25 ± 7.22	42.20 ± 9.63	40.60 ± 9.09	3.547•	0.018	S
Sex	Male	8 (40.0%)	2 (10.0%)	0 (0.0%)	0 (0.0%)	19.657*	0.000	HS
	Female	12 (60.0%)	18 (90.0%)	20 (100.0%)	20 (100.0%)			
Smoking	Yes	3 (15.0%)	1 (5.0%)	0 (0.0%)	0 (0.0%)	6.316*	0.097	NS
	No	17 (85.0%)	19 (95.0%)	20 (100.0%)	20 (100.0%)			

P-value >0.05: Non-significant (NS); P-value <0.05: Significant (S); P-value < 0.01: highly significant (HS); *: Chi-square test; •: One Way ANOVA test

Table (3): Comparison between studied groups as regard thyroid function tests.

		Control group	SLE group	RA group	SSC group	Test value	P-value	Sig.
		No. = 20	No. = 20	No. = 20	No. = 20			
TSH (mU/L)	Median (IQR)	2.37 (1.91 - 2.86)	2.26 (1.4 - 3.28)	2.04 (1.56 - 2.82)	2.53 (1.87 - 3.4)	1.071‡	0.784	NS
T3 (ng/dL)	Mean ± SD	2.66 ± 0.61	2.67 ± 0.72	2.61 ± 0.50	2.98 ± 0.02	0.436•	0.728	NS
T4 (ng/dL)	Mean ± SD	1.28 ± 0.29	1.23 ± 0.24	1.18 ± 0.21	1.66 ± 0.26	2.099•	0.107	NS

P-value >0.05: Non-significant (NS); P-value <0.05: Significant (S); P-value < 0.01: highly significant (HS); •: One Way ANOVA test; ‡: Kruskal Wallis test

Table (4): Comparison between studied groups as regard Tg Ab and TPO Ab.

		Control group		SLE group		RA group		SSC group		Test value*	P-value	Sig.
		No.	%	No.	%	No.	%	No.	%			
Tg Ab	Positive	3	15.0%	5	25.0%	2	10.0%	6	30.0%	3.125	0.373	NS
	Negative	17	85.0%	15	75.0%	18	90.0%	14	70.0%			
TPO Ab	Positive	3	15.0%	5	25.0%	2	10.0%	6	30.0%	3.125	0.373	NS
	Negative	17	85.0%	15	75.0%	18	90.0%	14	70.0%			

P-value >0.05: Non-significant (NS); P-value <0.05: Significant (S); P-value < 0.01: highly significant (HS); *: Chi-square test

Table (5): Comparison between studied groups as regard presence or absence of thyroid diseases.

Thyroid	Control group		SLE group		RA group		SSC group		Test value*	P-value	Sig.
	No.	%	No.	%	No.	%	No.	%			
With	3	15.0%	6	30.0%	1	5.0%	5	25.0%	4.841	0.184	NS
Without	17	85.0%	14	70.0%	19	95.0%	15	75.0%			

P-value >0.05: Non-significant (NS); P-value <0.05: Significant (S); P-value < 0.01: highly significant (HS); *: Chi-square test

Table (6): Comparison between SLE group with positive thyroid Abs & with negative thyroid Abs as regard disease activity measured by SLEDAI score and SLICC/ACR damage index.

		Tg Ab & or TPO				Test value*	P-value	Sig.
		Positive		Negative				
		No. = 5	25%	No. = 15	75%			
SLEDAI	Median (IQR)	14 (7 – 16)		8 (4 – 14)		0.833 [‡]	0.405	NS
SLICC/ACR	Median (IQR)	1 (0 – 3)		1.0 (0 – 2)		0.548 [‡]	0.584	NS

‡: Mann-Whitney test

Table (7): Comparison between SSC group with positive thyroid Abs & with negative thyroid Abs as regard Rodnan modified index and Medsger index.

		Tg Ab & or TPO		Test value•	P-value	Sig.
		Positive	Negative			
		No. = 6	No. = 14			
Rodnan modified index	Mean ± SD	12.67 ± 3.58	13.43 ± 3.77	-0.223	0.826	NS
Medsger index	Mean ± SD	1.67 ± 0.82	1.64 ± 0.63	0.071	0.944	NS

•: Independent t-test

Table (8): Comparison between RA group with positive thyroid Abs & with negative thyroid Abs as regard DAS 28 & HAQ score.

		Tg Ab & or TPO		Test value•	P-Value	Sig.
		Positive	Negative			
		No.2	No.18			
DAS 28	Mean ± SD	5.31 ± 1.06	4.30 ± 1.19	1.153	0.264	NS
HAQ score	Mean ± SD	2.00 ± 0.00	1.67 ± 0.77	0.600	0.556	NS

•: Independent t-test

DISCUSSION

Clustering of specific autoimmune diseases such as thyroiditis and systemic autoimmune diseases such as rheumatic diseases in the same patient is commonly noted, although the reasons for these associations are not completely clear. A common genetic background is one of the

proposed explanations for this link. Another explanation that has been put forward is that there may have been an exposure to a common triggering event such as a pollutant or a viral infection. In this regard, infections due to the Epstein-Barr virus and tobacco exposure have been implicated in both situations ⁽¹⁶⁾.

In the present study, we aimed to estimate the prevalence of thyroid autoantibodies among patients with systemic rheumatic diseases (SLE, RA and SSc) with or without clinical thyroid disorders and its association with disease activity and functional impairment.

In the current study, we found that 90% of SLE recruited patients were females, 100% of RA & SSc patients were females and it was 60% in the control group. This agrees with **Posselt et al.** ⁽¹⁶⁾, who evaluated the prevalence of thyroid autoantibodies in patients with systemic autoimmune rheumatic diseases and found that female gender in SLE patients was 93.6%, in RA patients was 90.9%, in SSc patients was 94.8% and control group was 92.1%. The previous findings confirm that female sex is predominant in RA, SLE and SSc patients.

In the current study, we found that SSc patients' mean age was 40.60±9.09 years, versus 35.80±9.83 years for control subjects. This agrees with **Shahin et al.** ⁽¹⁷⁾, who evaluated prolactin and thyroid hormones in 23 systemic sclerosis patients; and found that their mean age was 37.7±12.7 years versus 35.6±8.2 years for 15 normal control subjects.

In the current study, we found that the mean serum level of FT4 in SSc patients was 1.66±1.26 ng/dl and in control group 1.28±0.29 ng/dl. That was different from **Shahin et al.** ⁽¹⁷⁾, who found that mean serum levels of FT4 in SSc patients was 7.46±2.7 pmol/L (equal to 0.579 ng/dl) and in controls was 10.47±2.5 pmol/L (equal to 0.813 ng/dl). These variations might be due other co-morbidities in their patients.

Thyroid dysfunction is common in SLE and RA. Many are initially treated for thyroid dysfunction before the diagnosis of lupus or rheumatoid is made or vice versa ⁽¹⁸⁾. The prevalence of thyroid disorders (hypothyroidism and hyperthyroidism) in our study was 30% in SLE patients, 5% in RA patients, 25% in SSc patients and 20% in control group. So, prevalence of thyroid disorders in SLE and SSc patients were more than that of RA, however, there was no statistically significant difference between studied groups as regard presence or absence of thyroid diseases. On the other hand, **Lin et al.** ⁽¹⁹⁾ reported that the prevalence of thyroid disease was 8.1% & 16.9% in SLE patients and controls respectively, while **Appenzeller et al.** ⁽²⁰⁾ found that thyroid disease (predominantly hypothyroidism) was observed in 6.1% and 2% in SLE patients and controls respectively. The variations between the previous two studies and our study might be due to different sample sizes and racial variations.

Our results were also variable from **El-Hadidi et al.** ⁽²¹⁾, who found that the prevalence of thyroid dysfunction was more among lupus patients than controls (18% vs. 4%), and also from **El Sherif et al.** ⁽²²⁾, who evaluated thyroid disorders and autoantibodies in SLE and RA patients and found that thyroid disorders (hypothyroidism and hyperthyroidism) were significantly more common in SLE patients (50%) than in RA patients (15%).

The prevalence of hypothyroidism in our study was (25%), (5%), (15%) and (15%) in SLE, RA, SSc patients and control group respectively. This was different from **Watad et al.** ⁽²³⁾, who found that the proportion of hypothyroidism in SLE patients was 15.58% versus 5.75% in controls, and from **Shahin et al.** ⁽¹⁷⁾, who found that hypothyroidism was 33.3% in 23 SSc patients. Also, **Posselt et al.** ⁽¹⁶⁾, who found that the prevalence of hypothyroidism was (16.2%), (16.1%), (27.5%) and (11.3%) in SLE, RA, SSc patients and control group respectively.

Regarding SLE, our findings were higher than **Franco et al.** ⁽³⁾ and **Mader et al.** ⁽²⁴⁾, who found that the prevalence of hypothyroidism was 12% and 11.6% respectively in their cohort studies. The differences in these results could be explained by racial differences, region variations, patient selection (age and sex), size of sample, duration of follow up, influence of medications and diagnostic methods for the detection of thyroid disorders. Patients were on high-dose corticosteroids and other immunosuppressive drugs owing to their higher disease activity, indicating a possible role of these drugs on such type of thyroid dysfunctions.

In the current study, we have found that antithyroid antibodies (ATA) in SLE and SSc patients with or without thyroid disorders were higher than RA patients and healthy controls. ATA were positive in 25% of SLE patients, 30% of SSc patients and 10% of RA patients while were positive in 15% of control subjects. This agrees with **Przygodzka and Filipowicz-Sosnowska** ⁽²⁵⁾, who found that AbTg was positive in 12%, AbTPO was positive in 15% of RA patients and AbTg was positive in 9%, AbTPO was positive in 18% of controls. Our results were near to **Posselt et al.** ⁽¹⁶⁾, who reported that the prevalence of thyroid antibodies at least one antithyroid antibodies (ATA) was (32.8%), (19.5%), (36.2%) & (16.3%) in SLE, RA, SSc patients and control group respectively.

In our study, it was found that SLE patients were positive for Tg antibodies & TPO antibodies 1.6 times more than healthy controls. These findings were different from **Pan et al.** ⁽²⁶⁾, who found that their SLE patients were positive for Tg antibodies 2.9 times and TPO antibodies 2.2 times

more than healthy controls. While our findings were quite near to **Kumar et al.** (27), who found that the prevalence of Thyroid Ab was positive in 30% of 100 SLE patients and 10% of 100 controls.

An American cohort study was done by **Pyne and Isenberg** (28) to assess autoimmune thyroid disease in SLE; it was found that patients with thyroid disorders had higher prevalence of antithyroid antibodies (66%) than patients with normal thyroid functions, confirming the coexistence of the SLE and ATD. In a study done by **Shahin et al.** (17), who assessed AbTg in 45 SLE patients & 20 controls; it was found that AbTg was positive in 18.5% of SLE patients & 0% of controls. Another Latin American study done by **Innocencio et al.** (29); it was found that anti-Tg and anti-TPO were positive in 52% of SSc and 3.5% of controls which confirms a high prevalence of thyroid autoantibodies in SSc. Another meta-analysis study done by **Pan et al.** (26); they found that thyroid Abs were positive in 95% of SLE patients & 5% of healthy controls. Our results agreed with a study done by **Chan et al.** (30), who found that there was a higher prevalence of anti-TPO Abs and anti-Tg Abs in SLE patients than in the control group. Although different methods of testing for TAbs in different studies and differences in iodine intake between different areas might explain some of the discrepancy (31).

We aimed to assess the association between the prevalence of thyroid autoantibodies among patients with systemic rheumatic diseases with or without clinical thyroid disorders and its relation to disease activity and functional impairment. We found no statistically significant difference between SLE patients with positive & negative thyroid Abs as regard SLEDAI score and SLICC/ACR damage index. No statistically significant difference was found between RA patients with positive & negative thyroid Abs as regard DAS 28 score and HAQ score. And, no statistically significant difference in SSc patients with positive & negative thyroid Abs as regard Rodnan modified index and Medsger index. This agrees with **Posselt et al.** (16), who found that there was no statistically significant difference as regard SLEDAI and SLICC/ACR between SLE patients with positive & negative thyroid Abs, no statistically significant difference between RA patients as regard DAS 28 score or HAQ score with positive & negative thyroid Abs, and no statistically significant difference as regard Rodnan modified index and Medsger index in SSc group with positive & negative thyroid Abs. Our findings were confirmed by **Tekaya et al.** (32), who found that there were no significant differences in the DAS-28 between the RA patients with and without

thyroid abnormalities. On the contrary, **Koszarny et al.** (33), described thyroid autoantibodies as being more common in RA patients with high DAS-28 and the mean of DAS-28 was significantly higher in the TPO positive patients. Also, **Joshi et al.** (34) found that RA patients with hypothyroidism had higher DAS28-ESR and significant correlations were observed between TSH levels and ESR as well as DAS28-ESR. In contrast, **Przygodzka and Filipowicz-Sosnowska** (25) found that RA patients with thyroid disorders had a lower disease activity assessed using the DAS-28 than RA patients without thyroid disorders.

CONCLUSION

It could be concluded that the prevalence of thyroid autoantibodies; anti-thyroglobulin (Tg Ab) and anti-thyroid peroxidase (TPO Ab) and thyroid disorders in SLE and SSc patients are higher than RA patients with and without thyroid disorders. No link could be established between the presence of thyroid autoantibodies and the results from any of the instruments used to measure inflammatory activity and functional impairment in these cases of rheumatic diseases.

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