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FREQUENCY OF AUTOIMMUNE THYROID DISEASE AND THYROID DYSFUNCTION IN SYSTEMIC LUPUS ERYTHEMATOSUS AND ITS RELATIONSHIP WITH CLINICAL FINDINGS

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Abstract

Aim: Thyroid dysfunction (TD) and autoimmune thyroid disease (AITD) are frequently reported in patients with systemic lupus erythematosus (SLE). The relationship between SLE disease activity and thyroid disease is controversial. In this study, we aimed to investigate the frequency of TD and AITD in patients with SLE and their relationship with clinical findings and disease activity.

Material and Methods: Two hundred SLE patients between the ages of 18 and 75 years, who were followed in the rheumatology outpatient clinic and met the revised 1997 American College of Rheumatology (ACR) SLE classification criteria, were included in the study. Demographic, clinical, and laboratory data of the patients were obtained from patient files and hospital databases. The SLE Disease Activity Index (SLEDAI)- 2 K was used to evaluate SLE disease activity, and the Systemic Lupus International Collaborating Clinics (SLICC)/ACR Damage Index was used to assess damage.

Results: AITD was detected in 18.5% of patients with SLE, and 26.5% had TD. Neurological involvement (p=0.017), lymphopenia (p=0.016), hemolytic anemia (p=0.006) and direct coombs positivity (p=0.034) were found to be higher in patients with TD. Female gender (p=0.005), hemolytic anemia (p=0.001), antiphospholipid antibodies (aPL) (p=0.032) and direct coombs positivity (p=0.023) were more common in patients with AITD. When the risk factors were examined, it was determined that neurological involvement [odds ratio (OR)= 6.5], hemolytic anemia (OR= 4.6) and direct coombs positivity (OR= 2.2) increased the risk of TD, whereas aPL positivity and low complement decreased the risk. It was observed that the risk of AITD increased 5.2-fold in the presence of hemolytic anemia. A borderline significant increase in disease activity was observed in patients with TD (p=0.049). When a limit 6 was used for the SLEDAI score, activity was found to be higher in patients with TD (p=0.036).

Conclusion: Neurological involvement, hemolytic anemia, and direct Coombs positivity are risk factors for the presence of TD and AITD in SLE.

Keywords: Systemic lupus erythematosus, thyroid dysfunction, autoimmune thyroid disease

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INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic, autoimmune disease with multisystem involvement. SLE affects many organs, including the skin, joints, kidneys, nervous system, lungs and cardiac system (1). SLE is a multifactorial disease whose etiology is not well known, and genetic, hormonal, immunological and environmental factors play a role in its etiology.

Thyroid hormones may affect clinical findings in SLE, and conversely, SLE may cause changes in thyroid function. The relationship between SLE and thyroid diseases was first described in 1961 by White et al. (2) and Hijmans et al. (3). Studies have shown that the presence of thyroid dysfunction (TD) is more common in SLE patients than in the general population (4).

Most studies in the literature show that the prevalence and incidence of hypothyroidism and autoimmune thyroiditis are high in patients with SLE, especially in women. A limited number of cases of Graves' disease have also been reported in patients with SLE (5).

Studies have investigated whether there is a relationship between TD and different clinical findings of SLE, but most have reported that there is no significant relationship between TD and thyroid autoimmunity and the clinical and serological features of SLE (5). The results of studies evaluating TD and SLE are controversial.

The presence of TD in SLE patients may be due to euthyroid sick syndrome due to underlying systemic disease or the effects of drugs such as corticosteroids and immunosuppressives. Because both SLE and autoimmune thyroid disease (AITD) are seen in similar populations, it is a matter of debate whether SLE is an independent risk factor for TD or whether it is an incidental finding (6).

This study aimed to investigate the frequency of TD and AITD in patients with SLE and their relationship with clinical findings and disease activity.

MATERIAL AND METHODS

Four hundred patients aged 18-75 who were followed up in the rheumatology outpatient clinic between 2002 and 2022 and were diagnosed with SLE according to revised American College of Rheumatology (ACR) criteria were included in the study (7). Two hundred of these patients were excluded from the study according to the exclusion criteria. Demographic data, clinical findings, laboratory data, and medications of the patients included in the study were recorded in preprepared patient forms from the patients' clinic follow-up filesand hospital database. Patients without sufficient data due to lack of follow-up, who were pregnant when their thyroid functions were checked, and those without a thyroid function test were excluded from the study.

Patients with abnormal thyroid function tests and those who used levothyroxine (LT4) due to AITD and had normal thyroid function tests were classified as the TD group. Ten patients who were diagnosed with AITD based on ultrasonography findings and thyroid antibody positivity, who did not use LT4 and had normal thyroid function tests, were not included in the group of patients with TD. Disease activity scores at the time of thyroid function tests were calculated using the SLE Disease Activity Index (SLEDAI)-2K (0 inactive, 1-5 mild, 6-10 moderate, 11-19 high, >20 very highly active) (8). Laboratory parameters included in the disease activity score were obtained from patient examinations within the last month. The Systemic Lupus International Collaborating Clinics (SLICC)/ACR Damage Index was used to calculate damage (maximum 47 points) (9). Study protocol was approved by Kocaeli University Local Ethics Committee (ethics approval number: GOKAEK-2019/22.08)

Statistical Analysis

Statistical evaluation was performed using SPSS 20.0 (IBM Corp, Armonk, NY, USA) package program. Compliance with normal distribution was determined by the Kolmogorov-Smirnov test. Since the normal distribution assumption could not be met, numerical variables were given as median (25^{th}-75^{th} percentile). Categorical variables are given as the frequency (percentage). Differences between groups were determined by the Mann-Whitney U test. Relationships between categorical variables were determined using chi-square analysis. Binary logistic regression analysis was used to determine the factors affecting the outcome variable. In the hypothesis tests, $p<0.05$ was considered sufficient for statistical significance.

RESULTS

Of the 200 SLE patients included in the study, 175 were women (87.5%), and the age of the patients was 48.57±13.27 (minimum-maximum: 21-75). Demographic data of the patients are given in Table 1.

Mucocutaneous involvement was detected in 71.5% of the patients, joint involvement in 62%, serositis in 23%, kidney involvement in 43.5%, neurological involvement in 11%, hematological involvement in 87%, and immunological involvement in 73.5%. Antinuclear antibody was positive in all patients, 125 (62.5%) had low complement and 79 (39.5%) had direct Coombs positivity. In addition, antiphospholipid syndrome (APS) was detected in 20.5% of the patients, heart valve disease in 51%, pulmonary arterial hypertension in 6%, and avascular

Table 1. Demographic characteristics and clinical findings of the patients

n (%)	n=200
Gender (woman)	175 (87.5)
Age (years) mean ± Std (median; 25-75)	48.57±13.27 (49; 39-57.75)
Age of disease onset (years) mean ± Std (median; 25-75)	35.49±13,32 (34.5; 25-44)
Disease duration (years) mean ± Std (median; 25-75)	13.09±8.46 (12; 6-18)
Follow-up duration (years) mean ± Std (median; 25-75)	9.27±5.35 (8; 5-13)
Mucocutaneus Photosensitivity Malar rash Discoid rash	143 (71.5) 75 (37.5) 96 (48) 29 (14.5)
Joint involvement	124 (62)
Serositis	46 (23)
Neurological involvement	22 (11)
Kidney involvement	87 (43.5)
Hematological involvement Leukopenia Lymphopenia Hemolytic anemia Thrombocytopenia	174 (87) 124 (62) 138 (69) 13 (6.5) 78 (39)
Immunological involvement Anti-dsDNA Anti-Smith	147 (73.5) 130 (65) 24 (12)
Lung involvement	9 (4.5)
Antiphospholipid syndrome Anticardiolipin antibody Anti-β2 glycoprotein Lupus anticoagulant	41 (20.5) 36 (18) 26 (13) 31 (15.5)
Heart valve disease Aortic regurgitation Mitral regurgitation Tricuspid regurgitation	102 (51) 26 (13) 56 (28) 73 (36.5)
Pulmonary arterial hypertension	12 (6)
Avascular necrosis	27 (13.5)
Comorbidite Diabetes Ischemic heart disease Malignancy	32 (16) 20 (10) 8 (4) 8 (4)
Treatment Hydroxychloroquine Corticosteroid Mycophenolate mofetil Azathioprine Cyclophosphamide Cyslosporine Methotrexate Rituximab	 174 (87) 156 (78) 65 (32.5) 72 (36) 4 (2) 2 (1) 2 (1) 10 (5)

Std: Standard

necrosis in 13.5% (Table 2). When the thyroid function tests of the patients were performed, the median SLEDAI was calculated as 4 (Q1-Q3=0-6) and SLICC was calculated as 3 (Q1-Q3=1-4).

Thirty-seven (18.5%) SLE patients had AITD, 34 (17%) had Hashimoto thyroiditis, and 3 (1.5%) had Graves disease. According to laboratory results, TD was detected in 35 patients [high thyroid stimulating hormone (TSH) in 29 patients and low TSH in 6 patients]. Apart from these patients, 18 patients were using LT4 due to AITD (17 Hahimoto, 1 Graves patient), and the thyroid function tests of these patients were normal. There were no patients with T3 or T4 abnormalities. As a result, 53 patients were considered to have TD. Anti-thyroid peroxidase (anti-TPO) was positive in 31 (15.5%) patients, anti-thyroglobulin (anti-TG) was positive in 36 (18%) patients, and both antibodies were positive in 19 (9.5%) patients. Anti-TSHR antibody was tested in only 23 patients, and 7 (30%) of them were positive (Table 2). In addition, 13 (6.5%) patients had non-autoimmune hypothyroidism.

When the disease activities were examined according to SLEDAI at the time when the thyroid function tests of the patients were examined, it was observed that 58 (29%) patients were in remission. Mild activation was observed in 85 (42.5%), moderate in 50 (25%), high in 6 (3%) of the patients and very high in only one patient. When the damage index of that period was examined, no damage was detected in 18 (9%) of the patients, whereas the damage index was below 10 in all the remaining patients (score 1-2 in 38%, 3-4 in 40%, 5-6 in 11%, and 7-8 in 2%).

Table 2. Laboratory findings and diagnoses of patients regarding thyroid function

n (%)	n=200
High TSH	29 (14.5)
Low TSH	6 (3.0)
High T3	6 (3.0)
High T4	6 (3.0)
Anti-TPO positivity	31 (15.5)
Anti-TG positivity	36 (18.0)
Anti-TSHR positivity	7 (3.5)
Thyroid dysfunction	53 (26.5)
Hashimoto thyroiditis	34 (17)
Graves' disease	3 (1.5)
Multinodular goiter	5 (2.5)
LT4 usage	45 (22.5)

TSH: Thyroid stimulating hormone, T3: Triiodothyronine, T4: Thyroxine, Anti-TPO: Antithyroid peroxidase, Anti-TG: Anti-thyroglobulin, LT4: Levothyroxine

94.3% of the patients with TD and 85% of those without TD were female (p=0.130). When compared in terms of clinical involvement of SLE, no significant difference was found between those with and without TD in any involvement other than neurological involvement (20.8% vs. 7.5%; p=0.017, respectively). In terms of laboratory findings related to SLE, lymphopenia (83% vs. 63.9; p=0.016, respectively), hemolytic anemia (15.1% vs. 3.4%; p=0.006, respectively), and direct Coombs positivity (54.7% vs. 36.5%; p=0.034, respectively) were observed to be higher in the TD group. While no difference was detected in the SLICC score, a borderline increase in the SLEDAI score was detected in those with TD (median 4 vs. 3; p=0.049). When the SLEDAI score was grouped as <6 and ≥6, activity was found to be higher in those with TD (22.4% with SLEDAI <6, 36.8% with ≥6; p=0.036).

All 37 patients diagnosed with AITD were female (100% vs. 85%; p=0.005). When comparing patients with and without AITD in terms of SLE-related clinical findings, no significant difference was detected in any involvement. There was no significant difference in laboratory findings except for hemolytic anemia (19% vs. 3.6%; p=0.001), direct Coombs positivity (56.7% vs. 35.5%; p=0.023), and aPL (10.8% vs. 27.6%; p=0.032) positivity. In addition, it was observed that the activity and damage scores were similar in the groups with and without AITD.

When the factors associated with TD in patients with SLE were examined, only neurological involvement, APS, hemolytic anemia, direct Coombs positivity, and low complement were found to be significant. Among these factors, it was found that APS reduced the risk by 5.29 times (p=0.035), and low complement decreased the risk by 3.75 times (p=0.002). It was shown that neurological involvement [odds ratio (OR)=6.5; p=0.005), hemolytic anemia (OR=4.6; p=0.037) and direct coombs positivity (OR= 2.2; p=0.038) increased the risk of TD. When factors related to AITD were evaluated in SLE patients, only the presence of hemolytic anemia was found to be significant. It was determined that hemolytic anemia increased the risk of AITD by 5.29 times (p=0.026) (Table 3).

Table 3. Factors associated with thyroid dysfunction and autoimmune thyroid disease

	OR (95% confidence interval)	p value
Thyroid dysfunction		
Antiphospholipid syndrome	0.189 (0.04-0.88)	0.035
Neurological involvement	6.525 (1.78-23.81)	0.005
Hemolytic anemia	4.660 (1.09-19.75)	0.037
Low complement	0.266 (0.11-0.61)	0.002
Direct Coombs positivity	2.277 (1.04-4.95)	0.038
Autoimmune thyroid disease		
Hemolytic anemia	5.296 (1.22-22.92)	0.026

OR: Odds ratio

DISCUSSION

The frequency of AITD and TD in SLE patients and their relationship with SLE findings have been examined in various studies, and conflicting results have been reported. In this study, we aimed to investigate the frequency of AITD and TD and the factors associated with them in our patients.

Thyroid disease is frequently reported in SLE, and it is stated that SLE patients with thyroid disease have a higher risk of serious complications such as renal and neurological involvement. It has been emphasized that the frequency of thyroid disease is significantly higher, especially in those who have another autoimmune disease (overlap syndrome) along with SLE (10,11). The most commonly reported TD is overt and subclinical hypothyroidism. Hypothyroidism is 5 times more common than SLE in the general population. In a meta-analysis, it was reported that hypothyroidism was higher in SLE patients than in the control group (OR= 2.93), and this difference was greater in subclinical hypothyroidism patients (OR= 5.67) (12).

While the frequency of autoimmune hypothyroidism is reported to be 15.4%, the frequency of non-autoimmune hypothyroidism is reported to be 0.3-28.6% in different studies (10,13). In another study, TD was reported at a rate of 36%, and half of these patients were reported to have AITD and the other half had non-AITD (6). In our study, TD was detected in 26.5% of patients, and 55% of these patients were associated with AITD, whereas 45% had non-AITD. Our frequency of TD was found to be compatible with the rates reported in the literature.

In the study of Liu et al. (10) (n=2800), it was reported that renal involvement (35.6% in those with thyroid disease, 27.9% in those without; p=0.024) and neurological involvement (respectively 21.7%, 14.2%; p<0.0001) were detected more frequently in SLE patients with thyroid disease. In our study, neurological involvement (respectively 20.8%, 7.5%; p=0.017), lymphopenia (respectively 83%, 63.9%; p=0.016) hemolytic anemia (respectively 15.1%, 3.4%; p=0.006), and direct Coombs positivity (respectively 54.7%, 36.5%; p=0.034) were found to be higher in patients with thyroid dysfunction. When the risk factors were examined, it was determined that neurological involvement (OR =6.5) hemolytic anemia (OR =4.6), and direct coombs positivity (OR =2.2) increased TD, whereas APS and low complement decreased it. This difference may be due to our small sample size.

AITD affects 5% of the general population and is reported in 1-60% of patients in studies conducted in the SLE group. It is known that more than one autoimmune disease may occur simultaneously in SLE and Sjogren's syndrome (SjS). In the presence of more than one autoimmune disease, AITD usually accompanies these diseases. The frequency of AITD in SLE has been reported at different rates in different countries, with the lowest rate reported in Brazil (1%) and the highest rate in India (60%). A study from Colombia reported this rate as 12% (13). In our study group, the frequency of AITD was 18.5% and was found to be similar to the rates in the literature.

Female gender, advanced age, smoking, rheumatoid factor (RF) positivity, presence of SjS, and skin and joint involvement are reported as factors associated with AITD in SLE (13). It has been reported that RF positivity and the presence of SjS are more common in SLE patients with AITD (14). In the study by Wei et al. (14), 38 SLE patients with AITD were compared with 190 SLE patients without AITD, and it was found that serositis increased the risk of AITD by 3.64 times (p=0.00), anti-dsDNA positivity (p=0.01) and low C3 (p=0.02) has been reported to reduce the risk (15). In this study, although a relationship was found between female gender, presence of hemolytic anemia, aPL and direct Coombs positivity, and AITD, regression analysis showed that only hemolytic anemia increased the risk of AITD by 5.2 times.

Hashimoto thyroiditis is the most common thyroid disease in patients with SLE and has been reported to be 2.68-12.6% in studies (16-18). Additionally, euthyroid sick syndrome has been reported in 47.8% of patients with SLE (16). It has been reported that mor anti-Smith positivity (p=0.04) was detected in SLE patients with Hashimoto thyroiditis (17). In our patients, in the AITD group, all patients had Hashimoto thyroiditis (17%) except three patients. There was no patient with euthyroid sick syndrome. Similar to the AITD group, a relationship was found between Hashimoto thyroiditis and female gender, presence of hemolytic anemia, aPL, and direct Coombs positivity.

Antithyroid antibody positivity is observed in patients with SLE. In a systemic literature review, it was reported that 1.5-100% of SLE patients had anti-TPO positivity and 0.9-82.3% had anti-TG positivity (6,13,19,20). In our SLE group, 15.5% of the patients were anti-TPO positive and 18% were anti-TG positive, which was consistent with these rates.

The results of studies evaluating the relationship between SLE activity and thyroid disease are controversial. TD and euthyroid sick syndrome in patients with SLE may be due to the effects of systemic disease or medications such as corticosteroids and immunosuppressives. Because both diseases are seen in similar populations, it is a matter of debate whether SLE is an independent risk factor for TD or whether it is an incidental finding (6). The relationship between hypothyroidism or AITD and SLE clinical activity has been described in a few studies (16). The SLEDAI score was higher in SLE patients with sick euthyroid syndrome (mean SLEDAI score was 10.11 in those with euthyroid syndrome, 6.69 in those without; p=0.03). Also, there was no difference in terms of disease duration (6). In a study in which the SLEDAI score was considered <6 or ≥6, it was stated that there was no difference between the two groups in terms of antithyroid antibody positivity and hypothyroidism frequency (14.8% vs. 6.6%, p=NS) (21). In our study, a borderline significant increase in the SLEDAI activity index was observed in patients with TD (p=0.049). There was no difference in activity and damage indices between the groups with and without AITD.

Study Limitations

The retrospective design of our study is one of our limitations. Although our number of patients is high compared with many studies conducted on this subject, our sample size is another limitation.

CONCLUSION

As a result, TD was detected in 26.5% of our patients, and AITD was detected in 18.5% of our patients. A positive relationship was found between TD and neurological involvement, direct Coombs positivity, and hemolytic anemia, and a negative relationship with APS and low complement. A positive relationship was found only between AITD and hemolytic anemia. When evaluated in terms of activity and damage, a borderline significant increase in the SLEDAI activity index was observed only in those with TD. Consequently, larger controlled, prospective studies are needed to elucidate the causal relationships between TD.

Ethics

Ethics Committee Approval: Study protocol was approved by Kocaeli University Local Ethics Committee (ethics approval number: GOKAEK-2019/22.08)

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: A.Y., Concept: A.C., A.Y., Design: A.Y., Data Collection or Processing: A.K., A.K., Ö.Ö.I., N.G., D.T.K, A.C., A.Y., Analysis or Interpretation: A.K., Ö.Ö.I., N.G., D.T.K, A.Y., Literature Search: A.K., A.Y., Writing: A.K., A.K., A.Y.

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