

The Prevalence of Thyroid Dysfunction in Patients With Systemic Lupus Erythematosus

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Abstract

Background: Systemic lupus erythematosus (SLE) is a multisystemic autoimmune disease caused by immune system-mediated tissue damage. Autoimmune thyroiditis (AT) is an organ-specific disease associated with production of a variety of antibodies such as antinuclear antibodies, anti-double-stranded DNA, anti-Ro antibodies and anti-cardiolipin antibodies.

Objectives: The aim of this study was to evaluate the prevalence of thyroid dysfunction and thyroid auto-antibodies in patients with SLE and its relation to SLE disease and other autoantibodies.

Patients and Methods: This was a case-control study. The study included a total of 88 patients with SLE and 88 age- and sex-matched healthy volunteers as control group. Two study groups were compared regarding thyroid function test, antinuclear antibody (ANA), antibodies to double-stranded DNA (dsDNA), anti-thyroglobulin antibody (anti-Tg), and anti-thyroid peroxidase (anti-TPO) antibody.

Results: The mean age of SLE patients and controls were 32.16 ± 9.19 and 32.48 ± 9.47 years, respectively ($P = 0.821$). Patients had significantly higher prevalence (43.2% vs. 23.9%; $P = 0.015$) and titers (221.8 ± 570.5 vs. 78.2 ± 277.2 ; $P = 0.036$) of antibodies to Tg compared to controls. The patients had significantly lower titers of T3 compared to controls (125.2 ± 35.6 vs. 136.2 ± 26.5 ; $P = 0.021$). The titers of T4, TSH and anti-TPO antibody did not differ significantly between the two study groups.

Conclusions: Thyroid dysfunction was not higher in SLE patients compared to healthy individuals. However, anti-Tg antibodies were higher in SLE patients. It has not yet been established that thyroid function tests should be performed routinely in SLE patients.

Keywords: Lupus Erythematosus Systemic, Thyroiditis Autoimmune Antibodies, Antithyroid

1. Background

Systemic lupus erythematosus (SLE) is a multisystemic autoimmune disease caused by immune system-mediated tissue damage. Manifestations of SLE can involve the skin, joints, kidney, central nervous system, cardiovascular system, serosal membranes and hematologic and immune systems. The disease is highly heterogeneous, with patients manifesting variable combinations of clinical features. In most patients with SLE, the disease is characterized by a waxing and waning clinical course, although some demonstrate a pattern of chronic activity. The molecular triggers of disease are not known, but the pathogenesis is understood including production of autoantibodies exhibiting multiple specificities, with reactivity with nucleic acid-binding proteins as a common feature. Immune complexes, along with immune system cells and soluble mediators, generate inflammation and tissue damage. Therapeutic approaches generally involve immunosuppression. SLE occurs much more frequently in females than males. Like Hashimoto's

thyroiditis and Sjögren's syndrome, female-to-male ratio is approximately 8:1 to 9:1 in adults, and most cases are diagnosed between the ages of 15 and 44 years (1, 2).

Autoimmune thyroiditis (AT) is an organ-specific disease associated with production of a variety of antibodies such as antinuclear antibodies, anti-double-stranded DNA, anti-Ro antibodies, anti-cardiolipin antibodies and others (3). Autoimmune thyroiditis typically produces a modest goiter as a result of glandular infiltration with lymphocytes, inflammatory changes in thyrocytes and fibrosis. The hypothyroid state caused by autoimmune thyroiditis is associated with increased TSH levels that further stimulates thyroid enlargement. Graves' disease is characterized by diffuse thyroid enlargement due to the action of thyroid stimulating immunoglobulins. Other forms of thyroiditis can also present with goitrous enlargement of the thyroid gland, including subacute, lymphocytic and acute (suppurative) thyroiditis (4).

The association between AT, thyroid dysfunction and SLE has been reported in several studies with conflicting conclusions (5-12). While some studies reported a higher prevalence of hyperthyroidism in SLE patients (5-7), others reported a higher prevalence of hypothyroidism (8-12). One controlled study could not demonstrate a significantly higher prevalence of hypothyroidism in patients with SLE (13). The prevalence of anti-thyroid antibodies (ATA), namely anti-thyroglobulin antibodies (ATg) and anti-thyroid peroxidase antibodies (TPO) was reported to be higher in patients with SLE (8-13). In most studies, the results were compared to the prevalence of these disorders in the general population and were independent from SLE disease activity.

2. Objectives

The present study was performed to evaluate the prevalence of thyroid dysfunction and thyroid autoantibodies in Iranian patients with SLE and to investigate its relation with SLE disease and other autoantibodies.

3. Patients and Methods

3.1. Patients

This was a cross-sectional observational, case-controlled study performed in Lupus Clinic of Hafez Hospital, a specialized, referral, teaching hospital affiliated to Shiraz university of medical sciences in Islamic Republic of Iran. The study was performed during a 7-month period from November 2009 to May 2010. We included a total of 88 consecutive lupus (SLE) patients diagnosed according to the ACR criteria published in 1997 and 88 age- and sex-matched healthy volunteers as control group.

The study protocol was approved by the institutional review board (IRB) of Shiraz university of medical sciences and the ethics committee with document No. 2834 approved at March 2009. All the participants gave their informed written consent.

Inclusion criterion was lupus diagnosis according to the ACR criteria with at least one year of disease duration (14). All lupus patients selected by one rheumatologist and if he or she had criteria for selection referred for study inclusion. SLE patients were not in a flare of their disease based on the SLE Disease Activity Index (less than 3). The exclusion criteria were patients with other immune-suppressed conditions such as diabetes mellitus, kidney or bone marrow recipients, those infected with human immunodeficiency virus (HIV) and those with primary immunodeficiency diseases such as X-linked agammaglobulinemia, severe combined immunodeficiency (SCID) and common variable immune deficiency (CVID), simultaneous rheumatic disease such as Sjogren's syndrome, rheumatoid arthritis (RA) and systemic sclerosis (SS) and those with malignancies. None of the healthy volunteers in control group had history of immunologic or rheumatic disease as well as allergy and thyroid diseases.

3.2. Study Protocol

All patients underwent clinical and laboratory evaluations at diagnosis and quarterly during the follow-up and followed and examined by one rheumatologist throughout the year.

Demographic and clinical information such as disease duration, disease manifestations at any time and laboratory data, were collected from all patients. For this study, we analyzed symptoms and clinical findings that could be attributed to both autoimmune thyroid disease and SLE activity (or treatment related), including fatigue, nervousness, trembling, heat or cold intolerance, weight change, hyper- or hyporeflexia, tachy- or bradycardia, menstrual abnormalities, muscle atrophy and edema.

The levels of TSH, total triiodothyronine (T3), total thyroxine (T4), antinuclear antibody (ANA), antibodies to double-stranded DNA (dsDNA), anti-thyroglobulin antibodies (anti-Tg) and anti-thyroid peroxidase (anti-TPO) were determined in all patients and controls. Standard enzyme-linked immunosorbent assay (ELISA) was used to screen ANA (ELISA, EIA-2395; DRG Diagnostic, Marburg, Germany) and dsDNA (ELISA, EIA-3356; DRG Diagnostic, Marburg, Germany). Total T3 (Total T3 RIA-kit, Immunotech, Prague, Czech Republic), total T4 (Total T4 RIA-kit, Immunotech, Prague, Czech Republic) and Anti-TPO (Anti-TPO RIA-kit, Immunotech, Prague, Czech Republic) were measured by radioimmunoassay method, while serum TSH (TSH IRIA-kit, Immunotech, Prague, Czech Republic) and anti-Tg (Anti-hTg IRIA-kit, Immunotech, Prague, Czech Republic) were evaluated by immunoradiometric assay methods. The results were compared between cases and controls. All intra-assay and inter-assay coefficients were less than 10%. All hormonal tests were performed in endocrine and metabolism research center with Gamma counter instrument (Kontron made by Austria), which is calibrated regularly by local representative company in IR Iran.

3.3. Statistical Analysis

All statistical analyses were performed using Statistical Package for Social Sciences version 17.0 (SPSS Inc., Chicago, IL, USA). Chi-square test was used for comparison of qualitative variables between both groups. All of the qualitative variables were checked for normal distribution in the case and control groups. The independent sample t-test was used for comparison of the mean variables. Pearson's correlation coefficient was used for evaluation of correlation between variables.

Data reported as means \pm SD for 95% CI with 5% degree of freedom. A P value $<$ 0.05 was considered statistically significant.

4. Results

A total of 88 SLE patients and 88 healthy age- and sex-matched individuals entered the study. Six (6.8%) of our study population were men and 82 (93.2%) women. The

mean age of SLE patients was 32.16 ± 9.19 years ranged from 18 to 62 years.

Table 1 compares the study findings between both study groups. There was not any significant difference between both study groups regarding age ($P = 0.821$) and sex ($P = 0.783$). About eighty one percent (81.8%) of patients group had positive results for ANA and 70.4 % for anti-dsDNA. Forty three lupus patients had positive findings for anti-Tg antibody compared to 23.9% in control group with significant P-value ($P = 0.015$). No significant difference between the two groups was found regarding anti-TPO antibody (31.8% vs. 22.7%; $P = 0.236$).

TSH levels were normal in 65.9% and 76.1%, high in 31.8% and 23.9% and low in 2.3% and 0% of patients and control

groups, respectively with non-significant P-value ($P = 0.161$).

T3 levels were normal in 85.2% and 80.7%, high in 13.6% and 19.3% and low in 1.1% and 0.0% of patients and control group, respectively with no significant P-value ($P = 0.373$). The titers of T4 did not differ significantly between the two study groups (7.63 ± 2.1 vs. 8.19 ± 1.82 ; $P = 0.054$).

We performed correlation analysis between the autoantibodies and thyroid function test in those with SLE (Table 2). ANA was positively correlated with dsDNA ($r = 0.320$, $P = 0.002$). In the same way, anti-TPO was positively correlated to anti-Tg ($r = 0.187$, $P = 0.018$). Anti-TPO antibodies were correlated positively with T3 ($r = 0.390$, $P < 0.0001$) and T4 ($r = 0.251$, $P = 0.018$). T3 and T4 were also correlated with each other positively ($r = 0.610$, $P < 0.0001$).

Table 1. Comparison Between SLE Patients and Control Group Regarding Demographics, Thyroid Function and Auto-Antibodies^{a,b}

Variables	Cases (n = 88)	Controls (n = 88)	P Value
Mean Age, y	32.16 ± 9.19	32.48 ± 9.47	0.821
Gender			0.783
Male, %	6 (6.8)	7 (8)	
Female, %	82 (93.2)	81 (82)	
ANA, %	72 (81.8)	5 (5.6)	< 0.001
dsDNA, %	62 (70.4)	2 (2.3)	< 0.001
Anti-TPO Ab	28 (31.8)	20 (22.7)	0.236
Anti-Tg Ab	38 (43.2)	21 (23.9)	0.015
TSH			0.161
Normal	58 (65.9)	67 (76.1)	
High	28 (31.8)	21 (23.9)	
Low	2 (2.3)	0 (0)	
T3			0.373
Normal	75 (85.2)	71 (80.7)	
High	12 (13.6)	17 (19.3)	
Low 1	(1.1)	0 (0)	
ANA titer, IU/mL	3111.5 ± 1872.3	167.16 ± 707.4	< 0.001
Anti dsDNA titer, IU/mL	14912.5 ± 11789.1	4726.4 ± 3159.9	< 0.001
Anti-TPO titer, IU/mL	81.2 ± 230.5	101.2 ± 326.2	0.638
Anti-Tg titer, IU/mL	221.8 ± 570.5	78.2 ± 277.2	0.036
TSH titer, mIU/L	3.38 ± 3.2	3.3 ± 5.2	0.970
T3 titer, ng/mL	125.2 ± 35.6	136.2 ± 26.5	0.021
T4 titer, ng/mL	7.63 ± 2.1	8.19 ± 1.82	0.054

^aAbbreviations: ANA, antinuclear antibody; Anti dsDNA, anti double stranded DNA; Anti-Tg Ab, anti-thyroglobulin antibodies; Anti-TPO Ab, anti-thyroid peroxidase antibodies; TSH, thyroid stimulating hormone.

^bData are reported as No (%) or means \pm SD for 95% CI with 5% degree of freedom.

Table 2. Correlation Between Autoantibodies and Thyroid Function Tests in 88 Patients With SLE^a

Variable	Correlation Coefficient	P Value
ANA		
dsDNA	0.320	0.002
Anti-TPO	0.080	0.461
Anti-Tg	0.008	0.943
TSH	0.008	0.941
T3	0.020	0.851
T4	0.129	0.231
dsDNA		
Anti-TPO	-0.7	0.479
Anti-Tg	0.166	0.028
TSH	-0.003	0.980
T3	-0.184	0.086
T4	-0.092	0.395
Anti-TPO		
Anti-Tg	0.187	0.081
TSH	0.023	0.833
T3	0.390	< 0.0001
T4	0.251	0.018
Anti-Tg		
TSH	0.098	0.364
T3	0.132	0.220
T4	0.046	0.671
TSH		
T3	0.041	0.708
T4	-0.092	0.394
T3		
T4	0.610	< 0.0001

^aAbbreviations: ANA, antinuclear antibody; Anti dsDNA, anti double stranded DNA; Anti-Tg Ab, anti-thyroglobulin antibodies; Anti-TPO Ab, anti-thyroid peroxidase antibodies; TSH, thyroid stimulating hormone.

5. Discussion

SLE is a multisystemic disease and can involve any organ in the body including the thyroid gland (15-18). In the other hand, because of its autoimmune nature, other autoantibodies such as anti-TPO and anti-Tg can be produced during the natural course of disease (8, 9). Several studies demonstrated that patients with SLE have increased prevalence of thyroid dysfunction and autoimmune thyroiditis (5-12). While some studies reported a higher prevalence of hyperthyroidism in SLE patients (5-7), others reported a higher prevalence of hypothyroidism (8-12). In this study, we investigated the prevalence of thyroid dysfunction in patients with SLE and compared it to healthy individuals. We found that patients with SLE have higher prevalence of anti-Tg antibodies. Our SLE series had higher titers of anti-Tg antibodies accompanied by lower titers of T3. This shows that patients with SLE are at increased risk of devel-

oping thyroid dysfunction, especially hypothyroidism. Our results are consistent with some previous studies (7-9) and are contrary to some others (5, 10, 12). A large scale study analyzed the association between SLE and thyroid disease. In this study, data collected during 2000 - 2009 and concluded that SLE patients had a lower rate of thyroid disease than matched control group (19, 20).

One controlled study that addressed this issue could not demonstrate a significantly higher prevalence of hypothyroidism in patients with SLE (13). The prevalence of anti-thyroid antibodies (ATA), namely anti-thyroglobulin antibodies (ATg) and anti-thyroid peroxidase antibodies (TPO) was reported to be higher in patients with SLE (8-13). In most studies, the results were compared to the prevalence of these disorders in the general population and were independent from SLE disease activity.

In this regards Antonelli et al. (10) evaluated the prevalence of clinical and subclinical thyroid disorders in patients with SLE compared with sex- and age-matched controls. Thyroid hormones and antithyroid antibodies were tested and thyroid ultrasonography was performed in 213 patients with SLE compared with 426 sex- and age-matched controls, from the same geographic area, with a well-defined status of iodine intake. The odds ratio for subclinical hypothyroidism for female patients with SLE with respect to controls was 4.5 (95% confidence interval [CI], 2.5-8.4), for antithyroid peroxidase antibody (AbTPO) positivity was 2.6 (95% CI, 1.7-4.1) and for thyroid autoimmunity 2.9 (95% CI, 2.0-4.4). The mean values of thyroid stimulating hormone and AbTPO were higher in female SLE patients than controls ($P < 0.01$). A significantly ($P < 0.01$) higher prevalence of clinical hypothyroidism and Grave's disease was observed in female SLE patients than controls. No significant difference between SLE patients and controls was detected regarding free triiodothyronine and thyroxine. It is suggested to assess thyroid function and AbTPOs and perform ultrasonography as part of the clinical profile in SLE patients. Subjects at high risk (women, positive AbTPOs, hypoechoic and small thyroid) should have thyroid function follow-up and appropriate treatment in due course (10).

Autoimmune thyroiditis is often accompanied by production of non-organ-specific antibodies. Some patients with this disease might develop systemic autoimmune disorders (3). Many systemic autoimmune disorders have been reported to be associated with autoimmune thyroiditis in up to 50% of cases. These disorders include SLE, rheumatoid arthritis, Sjogren's disease, mixed connective tissue disease and others. In particular, the incidence of SLE in Hashimoto thyroiditis was reported to be 6.5% compared to 0.05% - 0.1% in the general population (21).

In this regards, Al-Awadhi et al. (12) examined the frequencies of abnormal thyroid function tests and serum thyroid autoantibodies in healthy Kuwaitis and those with autoimmune diseases. Serum concentrations of sensitive thyrotropin and free thyroxine were measured in 577 apparently healthy controls, 177 patients with rheumatoid arthritis (RA), 60 with systemic lupus erythematosus (SLE) and 25 with primary Sjogren's syndrome (pSS). Serum microsomal and thyroglobulin autoantibodies were also measured. For analysis of thyroid function tests, the subjects were classified into five categories of normal, subclinical hypothyroidism, overt hypothyroidism, euthyroid sick syndrome and biochemical hyperthyroidism. Subclinical hypothyroidism was seen in 1.7% of healthy controls, 10.2% of RA, 13.3% of SLE and 16% of pSS patients. Among RA patients, the frequency of 9 subclinical hypothyroidism in females (11.4%) was significantly higher than males (5.4%; $P < 0.01$). In SLE and pSS patients, all those with subclinical hypothyroidism were females. Overt hypothyroidism was seen in 1.4% of controls, 10.2% of RA, 8.3% of SLE and 4% of pSS patients. Biochemical hyperthyroidism was seen in 0.2% of con-

trols, 4.5% of RA, 5% of SLE and none of pSS patients. The euthyroid sick syndrome was seen in 0.4% of controls, 13.6% of RA, 16.7% of SLE and none of pSS patients. Thyroid autoantibodies were present in 3.1% of controls, 12.4% of RA, 18.3% of SLE and 12% of pSS patients. These data showed that abnormal thyroid function tests and thyroid autoantibodies occur frequently in Kuwaitis with autoimmune diseases. Therefore, ordering these tests in these diseases is recommended (12).

The prevalence of thyroid dysfunction did not differ significantly between groups. However, in most studies, higher prevalence of hypothyroidism, either clinical or sub-clinical, was reported in patients with SLE. Many of these cases were also accompanied by elevated ATA suggestive of autoimmune thyroiditis (13). It was also found that the ATA levels correlated with serum levels of other SLE characteristic antibodies such as anti-Sm, ribonucleoprotein (RNP) and double stranded DNA antibodies (6). The pathogenesis of primary hypothyroidism is autoimmune in approximately 80% of cases. This notion can explain the results of previous studies showing that ATA was often elevated in SLE patients, and these patients had a higher prevalence of thyroid dysfunction, mainly clinical or subclinical hypothyroidism (22, 23).

In most studies, thyroid function tests and ATA in SLE patients were not measured in a control group and were compared to existing data in the general population (8). In this study, we compared the results of the study group to an age- and sex-matched control group. The prevalence of thyroid dysfunction did not differ significantly between the groups in our series. This can be due to this fact that all of our patients were in remission and none had disease activity score more than 3.

The prevalence of ATA in the study group was similar to the previously reported prevalence in SLE (7). The prevalence of ATA in a small control group and in an autopsy study was reported to be 27% in female patients without overt thyroid disease (13, 24, 25). However, a large Welsh study reported the prevalence of ATA as 10% in healthy individuals aged 18 - 45 years (26). This is similar to the data obtained in both our study and control groups and highlights the need for an appropriate control group. As autoimmune thyroiditis affects more often females than males, the absence of difference in the prevalence of ATA between our study group and the control group cannot be ascribed to the gender differences between the groups. Most SLE patients are treated with immunosuppressant medications. The effect of immunosuppressive therapy on production of ATA has not yet been elucidated. It could presumably reduce the production of antibodies, which might explain the paucity of ATA production in SLE patients (27).

The two main autoantibodies are ATg and TPO, with the latter being the most important and representative for autoimmune thyroiditis (14). A fluctuating course of ATA over time was reported in some SLE patients. It was shown that some patients with positive results for ATA at a certain

point during the course of their disease had negative results for one or more of the antibodies tested during follow-up visits. However, patients with persistently elevated ATA were more likely to develop thyroid diseases (23). The time when the tests are performed is therefore important when SLE patients are evaluated for ATA. However, this objective is beyond the scope of cross-sectional studies, like reported studies to date. In a 20-year follow-up study on the incidence of thyroid disease, it was found that the odds ratios for development of hypothyroidism in ATA-positive individuals were 8 for women and 25 for men (28).

Hrycek et al. showed that free T3 and free T4 concentrations were lower in lupus patients compared to control group (29). Kumar et al. (30) showed that primary and subclinical hypothyroidism is the most common thyroid disease in lupus patients and rarely hyperthyroidism occurs in these patients. He showed that 36% of lupus patients had thyroid disease (29). Franco et al. indicated that autoimmune thyroid disease in SLE is frequent and has no correlation with severity of disease (31). One meta-analysis by Pan et al. suggested that autoimmune thyroid disease is more prevalent in patients with lupus (20). It has not yet been established whether ATA fluctuates with the SLE disease activity. Mader et al. (9) showed that ATA levels did not correlate with the degree of disease activity measured by the SLEDAI score or with any component of the SLEDAI. Therefore, it can be assumed that production of ATA is unrelated to the disease activity. In our study, we performed thyroid tests in lupus patients and compared with normal population as control group, which is representative of our population as strength point. In contrast, our study had a small sample size and cross-sectional study as a weak point. More longitudinal prospective cohort studies are needed for more evaluation of the prevalence of thyroid dysfunction in SLE patients.

In conclusion, this cross-sectional study showed that thyroid dysfunction was not more prevalent in SLE patients compared to healthy individuals. However, anti-Tg antibodies were higher in our SLE patients. It has not yet been established that thyroid function tests should be performed routinely in SLE patients. However, testing ATA in euthyroid SLE patients seems unjustified. Larger controlled longitudinal studies are needed to elucidate the causal relationships between thyroid dysfunction, ATA, SLE and SLE disease activity. Larger sample size, presence of control group or a meta-analysis are needed for obtaining better results and be able to generalize them.

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Footnote

Authors' Contribution: Study concept and design: Mohammad Ali Nazarinia; acquisition of data: Mesbah Shams; analysis and interpretation of data: Eskandar

Kamali-Sarvestani; drafting of the manuscript: Nakisa Rasaei; critical revision of the manuscript for important intellectual content; statistical analysis: Mesbah Shams; administrative, technical, and material supports; study supervision: Mohammad Ali Nazarinia.

References

1. Mosca M, Bombardieri S. Disease-specific quality indicators, guidelines, and outcome measures in systemic lupus erythematosus (SLE). *Clin Exp Rheumatol*. 2007;**25**(6 Suppl 47):107-13. [PubMed: 18021515]
2. Griffiths B, Mosca M, Gordon C. Assessment of patients with systemic lupus erythematosus and the use of lupus disease activity indices. *Best Pract Res Clin Rheumatol*. 2005;**19**(5):685-708. doi: 10.1016/j.berh.2005.03.010. [PubMed: 16150398]
3. Tektonidou MG, Anapliotou M, Vlachoyiannopoulos P, Moutsopoulos HM. Presence of systemic autoimmune disorders in patients with autoimmune thyroid diseases. *Ann Rheum Dis*. 2004;**63**(9):1159-61. doi: 10.1136/ard.2004.022624. [PubMed: 15308528]
4. Delamere JP, Scott DL, Felix-Davies DD. Autoimmune thyroiditis. *J R Soc Med*. 2008;**102**:6. [PubMed: 18344462]
5. Goh KL, Wang F. Thyroid disorders in systemic lupus erythematosus. *Ann Rheum Dis*. 1986;**45**(7):579-83. [PubMed: 3740982]
6. Konstadoulakis MM, Kroubouzou G, Tosca A, Piperigos G, Marafelia P, Konstadoulakis M, et al. Thyroid autoantibodies in the subsets of lupus erythematosus: correlation with other autoantibodies and thyroid function. *Thyroidology*. 1993;**5**(1):1-7. [PubMed: 7508737]
7. Chan AT, Al-Saffar Z, Bucknall RC. Thyroid disease in systemic lupus erythematosus and rheumatoid arthritis. *Rheumatology (Oxford)*. 2001;**40**(3):353-4. [PubMed: 11285395]
8. Pyne D, Isenberg DA. Autoimmune thyroid disease in systemic lupus erythematosus. *Ann Rheum Dis*. 2002;**61**(1):70-2. [PubMed: 11779764]
9. Mader R, Mishail S, Adawi M, Lavi I, Luboshitzky R. Thyroid dysfunction in patients with systemic lupus erythematosus (SLE): relation to disease activity. *Clin Rheumatol*. 2007;**26**(11):1891-4. doi: 10.1007/s10067-007-0602-5. [PubMed: 17372671]
10. Antonelli A, Fallahi P, Mosca M, Ferrari SM, Ruffilli I, Corti A, et al. Prevalence of thyroid dysfunctions in systemic lupus erythematosus. *Metabolism*. 2010;**59**(6):896-900. doi: 10.1016/j.metabol.2009.10.010. [PubMed: 20005534]
11. Appenzeller S, Pallone AT, Natalin RA, Costallat LT. Prevalence of thyroid dysfunction in systemic lupus erythematosus. *J Clin Rheumatol*. 2009;**15**(3):117-9. doi: 10.1097/RHU.0b013e31819dbe4c. [PubMed: 19300286]
12. Al-Awadhi AM, Olusi S, Hasan EA, Abdullah A. Frequency of abnormal thyroid function tests in Kuwaiti Arabs with autoimmune diseases. *Med Princ Pract*. 2008;**17**(1):61-5. doi: 10.1159/000109592. [PubMed: 18059103]
13. Weetman AP, Walport MJ. The association of autoimmune thyroiditis with systemic lupus erythematosus. *Br J Rheumatol*. 1987;**26**(5):359-61. [PubMed: 3664160]
14. Smith EL, Shmerling RH. The American College of Rheumatology criteria for the classification of systemic lupus erythematosus: strengths, weaknesses, and opportunities for improvement. *Lupus*. 1999;**8**(8):586-95. [PubMed: 10568894]
15. Hahn BH, Fauci AS, Braunwald EK DL, Hauser SL, Longo DL. Systemic lupus erythematosus. In: Fauci AS, Braunwald E, Kasper DL, Hauser SL, Longo DL, Jameson JL, et al., editors. *Harrison's Principals of Internal Medicine*. New York: McGraw-Hill; 2008. pp. 2075-83.
16. Mills JA. Systemic lupus erythematosus. *N Engl J Med*. 1994;**330**(26):1871-9. doi: 10.1056/NEJM199406303302608. [PubMed: 8196732]
17. Pisetsky DS. Systemic lupus erythematosus. *Med Clin North Am*. 1986;**70**(2):337-53. [PubMed: 3512930]
18. Arbuckle MR, McClain MT, Rubertone MV, Scofield RH, Dennis GJ, James JA, et al. Development of autoantibodies before the clinical onset of systemic lupus erythematosus. *N Engl J Med*. 2003;**349**(16):1526-33. doi: 10.1056/NEJMoa021933. [PubMed: 14561795]

19. Lin WY, Chang CL, Fu LS, Lin CH, Lin HK. Systemic lupus erythematosus and thyroid disease: A 10-year study. *J Microbiol Immunol Infect.* 2014. doi: 10.1016/j.jmii.2014.03.004. [PubMed: 24874431]
20. Pan XF, Gu JQ, Shan ZY. Patients with systemic lupus erythematosus have higher prevalence of thyroid autoantibodies: a systematic review and meta-analysis. *PLoS One.* 2015;10(4):e0123291. doi: 10.1371/journal.pone.0123291. [PubMed: 25905898]
21. Biro E, Szekanez Z, Czirjak L, Danko K, Kiss E, Szabo NA, et al. Association of systemic and thyroid autoimmune diseases. *Clin Rheumatol.* 2006;25(2):240-5. doi: 10.1007/s10067-005-1165-y. [PubMed: 16247581]
22. Vianna JL, Haga HJ, Asherson RA, Swana G, Hughes GR. A prospective evaluation of antithyroid antibody prevalence in 100 patients with systemic lupus erythematosus. *J Rheumatol.* 1991;18(8):1193-5. [PubMed: 1941823]
23. Kausman D, Isenberg DA. Thyroid autoimmunity in systemic lupus erythematosus: the clinical significance of a fluctuating course. *Br J Rheumatol.* 1995;34(4):361-4. [PubMed: 7788152]
24. Park DJ, Cho CS, Lee SH, Park SH, Kim HY. Thyroid disorders in Korean patients with systemic lupus erythematosus. *Scand J Rheumatol.* 1995;24(1):13-7. [PubMed: 7863271]
25. Yoshida H, Amino N, Yagawa K, Uemura K, Satoh M, Miyai K, et al. Association of serum antithyroid antibodies with lymphocytic infiltration of the thyroid gland: studies of seventy autopsied cases. *J Clin Endocrinol Metab.* 1978;46(6):859-62. doi: 10.1210/jcem-46-6-859. [PubMed: 263468]
26. Groves CJ, Howells RD, Williams S, Darke C, Parkes AB. Primary standardization for the ELISA of serum thyroperoxidase and thyroglobulin antibodies and their prevalence in a normal Welsh population. *J Clin Lab Immunol.* 1990;32(3):147-51. [PubMed: 1966952]
27. Miller FW, Moore GF, Weintraub BD, Steinberg AD. Prevalence of thyroid disease and abnormal thyroid function test results in patients with systemic lupus erythematosus. *Arthritis Rheum.* 1987;30(10):1124-31. [PubMed: 3675658]
28. Vanderpump MP, Tunbridge WM, French JM, Appleton D, Bates D, Clark F, et al. The incidence of thyroid disorders in the community: a twenty-year follow-up of the Whickham Survey. *Clin Endocrinol (Oxf).* 1995;43(1):55-68. [PubMed: 7641412]
29. Hrycek A, Hrycek E, Kopczynski P, Kopczynska M, Romanowski L, Walawska A. [The thyroid functional tests, antithyroid antibodies and the level of prolactin in treated patients with systemic lupus erythematosus]. *Pol Merkur Lekarski.* 2010;29(172):231-4. [PubMed: 21207638]
30. Kumar K, Kole AK, Karmakar PS, Ghosh A. The spectrum of thyroid disorders in systemic lupus erythematosus. *Rheumatol Int.* 2012;32(1):73-8. doi: 10.1007/s00296-010-1556-5. [PubMed: 20658291]
31. Franco J, Amaya-Amaya J, Molano-Gonzalez N, Caro-Moreno J, Rodriguez-jimenez M, Acosta-Ampudia Y, et al. Autoimmune thyroid disease in Colombian patients with systemic lupus erythematosus. *Clin Endocrinol (Oxf).* 2014. doi: 10.1111/cen.12662. [PubMed: 25382266]