

# THYROID FUNCTION AND ANTITHYROID AUTOANTIBODIES IN PATIENTS WITH CONNECTIVE TISSUE DISEASES

Irena Kostić<sup>1</sup>, Snežana Živančević-Simonović<sup>1</sup>, Mirjana Bukilica<sup>2</sup>, Ljiljana Dimitrijević<sup>3</sup>

<sup>1</sup>Institute of Pathophysiology, School of Medicine, University of Kragujevac, <sup>2</sup>Institute of Rheumatology, Belgrade, <sup>3</sup>Institute of Immunology and Virology – Torlak, Department of Research and Development, Vojvode Stepe 458, 11152 Belgrade, Serbia and Montenegro

## FUNKCIJA ŠTITASTE ŽLEZDE I PRISUSTVO ANTITIREOIDNIH AUTOANTITELA KOD BOLESNIKA SA SISTEMSKIM BOLESTIMA VEZIVNOG TKIVA

Irena Kostić<sup>1</sup>, Snežana Živančević-Simonović<sup>1</sup>, Mirjana Bukilica<sup>2</sup>, Ljiljana Dimitrijević<sup>3</sup>

<sup>1</sup>Institut za patološku fiziologiju, Medicinski fakultet, Univerzitet u Kragujevcu, <sup>2</sup>Institut za reumatologiju, Beograd, <sup>3</sup>Institut za imunologiju i Virusologiju – Torlak, Odeljenje za istraživanje i razvoj, Beograd, Srbija

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### ABSTRACT

Autoimmune thyroid disease (ATD) has been described in patients with connective tissue diseases (CTD). The aim of this study was to estimate and compare the prevalence of ATD in a group of 91 CTD patients, and in their subgroups: 53 systemic lupus erythematosus (SLE), 24 rheumatoid arthritis (RA), 7 primary Sjogren's syndrome (SSy) and 7 progressive systemic sclerosis (SSc) patients. A control group of 34 healthy blood volunteers was used for comparison. Serum levels of free thyroxine (FT4), thyroid stimulating hormone (TSH), as well as thyroid autoantibodies (Abs) specific of thyroperoxidase (TPO) and thyroglobulin (Tg) were examined. CTD patients, in general, as well as SLE and RA subgroups, had significantly higher number of thyroid dysfunction than the control group ( $p < 0.05$ ). The most prominent thyroid dysfunction was subclinical hypothyroidism, with a higher prevalence in all subgroups of patients when compared to the control. Anti-TPO Abs were detected in a significant number of CTD patients, especially in SLE subgroup when compared to the control group. It was also found that a higher number of CTD patients, SLE and RA subgroups, had positive anti-Tg Abs, when compared to the control subjects. In conclusion, the prevalence of ATD in CTD patients was more frequent than in the control group. The patients with anti-TPO Abs and anti-Tg Abs at the time when they were analyzed, had hyperthyroidism, hypothyroidism or were clinically and biochemically euthyroid. The prevalence of hypothyroidism was greater than the prevalence of hyperthyroidism in all subgroups of patients.

**Key words:** connective tissue disease, hyperthyroidism, hypothyroidism, autoantibodies

**Abbreviations:** Abs - antibodies, ATD - autoimmune thyroid disease, CTD - connective tissue diseases, DAS - Disease Activity Score, ECLAM - European Consensus Lupus Activity Measurement, FT4 - free thyroxine, RA - rheumatoid arthritis, SLE - systemic lupus erythematosus, SSc - systemic sclerosis, SSy - Sjogren's syndrome, Tg - thyroglobulin, TPO - thyroperoxidase, TSH - thyroid stimulating hormone

### SAŽETAK

Autoimunske bolesti štitaste žlezde (AITD) opisane su kod bolesnika sa sistemskim bolestima vezivnog tkiva (SBVT). Cilj ovog rada bio je da se ispita prevalencija AITD u grupi od 91 bolesnika sa SBVT, koja je uključila 53 bolesnika sa sistemskim eritemskim lupusom (SLE), 24 obolelih sa reumatoidnim artritisom (RA) i po 7 obolelih od primarnog Sjogrenovog sindroma (SSy) i progresivne sistemske skleroze (SSc). Kontrolnu grupu ispitanika činila su 34 dobrovoljna davaoca krvi. Kod svih učesnika u studiji merene su serumske koncentracije slobodnog tiroksina (FT4), tireostimulišućeg hormona (TSH), kao i autoantitela specifičnih za tireoperoksidazu (anti-TPO At) i tireoglobulin (anti-Tg At). U grupi bolesnika sa SBVT, kao i u podgrupama obolelih od SLE i RA, nađena je statistički značajno veća učestalost poremećaja funkcije štitaste žlezde u odnosu na kontrolnu grupu ( $p < 0.05$ ), a od svih poremećaja funkcije štitaste žlezde najčešće je detektovana subklinička hipotireoza. Anti-TPO At nađena su kod značajno većeg broja bolesnika sa SBVT i SLE, u odnosu na kontrolnu grupu. Isto tako, i anti-Tg At su detektovana kod većeg broja ispitanika u grupi SBVT, i podgrupama SLE i RA, nego kod zdravih osoba. U zaključku, prevalencija AITD kod obolelih od SBVT veća je nego u kontrolnoj grupi. Bolesnici sa anti-TPO At i anti-Tg At u vreme kada su analizirani, imali su subkliničku ili klinički manifestnu hipotireozu ili hipertireozu, ili su još bili u stadijumu bolesti u kome se ne može detektovati poremećaj funkcije štitaste žlezde. Prevalencija hipotireoze bila je veća od prevalencije hipertireoze u svim podgrupama bolesnika sa SBVT.

**Ključne reči:** sistemske bolesti vezivnog tkiva, hipertireoza, hipotireoza, autoantitela

**Skraćenice:** Abs - antibodies, ATD - autoimmune thyroid disease, CTD - connective tissue diseases, DAS - Disease Activity Score, ECLAM - European Consensus Lupus Activity Measurement, FT4 - free thyroxine, RA - rheumatoid arthritis, SLE - systemic lupus erythematosus, SSc - systemic sclerosis, SSy - Sjogren's syndrome, Tg - thyroglobulin, TPO - thyroperoxidase, TSH - thyroid stimulating hormone

### INTRODUCTION

The occurrence of ATD during the course of non-organ-specific CTD including SLE, RA, primary SSy and progressive SSc, is more frequent than previously believed (1). Since the first articles about the association of silent thyroiditis with SLE (2-4), RA (5,6), primary SSy (7,8) and progressive SSc (9,10) were reported, there has been an interest in detecting the prevalence of thyroid disturbances, as well as the presence of antithyroid autoantibodies in patients with CTD, even in those who did not have clinically overt thyroid disease. A number of up-to-date studies have suggested that thyroid disease is more common in CTD patients than in the general population, but the prevalence of hypothyroidism or hyperthyroidism is a heated topic of discussion (12, 13).

In this article the prevalence of both, the hypothyroid and hyperthyroid disease, together with the prevalence of antithyroid autoantibodies in the group of CTD patients, in SLE, RA, primary SSy, and progressive SSc subgroups, are reported.

### PATIENTS AND METHODS

Fifty-three SLE patients and twenty-four RA patients fulfilling four or more of the revised classification criteria of the American Rheumatism Association for these disorders were selected for the study. SLE disease activity was assessed using the European Consensus Lupus Activity Measurement (ECLAM). Patients from the RA group were found to be in a non-aggressive stage of disease based on the Disease Activity Score (DAS). All seven SSy patients in this study met the European consensus

criteria for Sjogren's syndrome and seven patients with progressive SSc satisfied one major or two minor classification criteria for SSc.

Patients with CTD were hospitalized or treated as outpatients at the Institute of Rheumatology in Belgrade or at the Department of Rheumatology of the Internal Medicine Clinic in Kragujevac. Patients with CTD who had a history of thyroid disease or patients who had used oral contraceptives, androgens, propranolol, lithium or amiodarone were excluded from this study. Thirty-four blood donors who had biochemically normal liver and kidney function and who did not show clinical signs of thyroid disease, nor had used the medications mentioned above, were included in the control group.

To estimate the thyroid function of CTD patients and control group subjects, the levels of FT4 and TSH were measured. The presence of antithyroid (anti-TPO and anti-Tg) autoantibodies was analyzed as indicative of autoimmune thyroid disease.

### Thyroid hormone levels

FT4 and TSH concentrations were measured using CIS Biointernational kits with the normal range 7–18 pg/ml and 0.25–4.0  $\mu$ IU/ml, respectively.

### Thyroid function assessments

According to the measured TSH and FT4 concentrations, subjects were considered euthyroid when FT4 and TSH levels were within the normal range; clinically hypothyroid when FT4 levels were subnormal while TSH levels were increased; subclinically hypothyroid when having normal FT4 levels and increased TSH levels; clinically hyperthyroid when FT4 levels were above normal and TSH levels were below normal range; and finally subclinically hyperthyroid when FT4 levels were normal while TSH levels were decreased.

### Detection of antithyroid autoantibodies

Anti-TPO Abs were detected using competitive radioligand assay (TPO-AB-CT, by CIS Biointernational). Serum samples with levels greater than 100 U/ml were considered positive. Anti-Tg Abs were determined using the immunoradiometric assay (ELSA -AB-hTG, by CIS Biointernational). Levels greater than 50 U/ml were considered positive.

### Statistical analysis

Chi-square, Fisher's exact probability test and two sample T-tests were applied where appropriate.

## RESULTS

### Thyroid function

The group of CTD patients included in this study was similar to the control group according to sex and mean age (table 1). The number of women was higher than the number of men in all studied subgroups. That was in agreement with epidemiological observations that in the middle-aged females CTD occurred more often.

**Table 1.** CTD patients according to disease, sex, age and thyroid function

	SLE	RA	SSc	SSy	CTD	control
patients (No.)	53	24	7	7	91	34
sex (F: M)	50:3	21:3	6:1	6:1	83:8	32:2
mean age $\pm$ SD (years)	43.49 $\pm$ 10.65	54 $\pm$ 9	44.14 $\pm$ 7.19	53 $\pm$ 8.5	47 $\pm$ 4.85	44.56 $\pm$ 9.71
thyroid dysfunction (No.)	12	5	1	1	19	1

Of 91 patients with CTD, 19 had abnormal thyroid function, which was significantly higher compared to the one subject in the control group ( $p < 0.05$ ). Similarly, the occurrence of thyroid function abnormalities in the subgroups of SLE and RA patients (12 and 5, respectively) were significantly higher than in the control group ( $p < 0.05$ ). The same number of SSc and SSy patients had thyroid abnormalities which was higher compared to the healthy controls, though not statistically significant (table 1).

The most frequent thyroid dysfunction was subclinical hypothyroidism which was detected in 11 of all CTD patients, in 6/53 patients with SLE, in 3/24 patients with RA and in one of SSc and SSy patients (table 2), and again it has a higher prevalence in all subgroups of patients when compared with the healthy subjects.

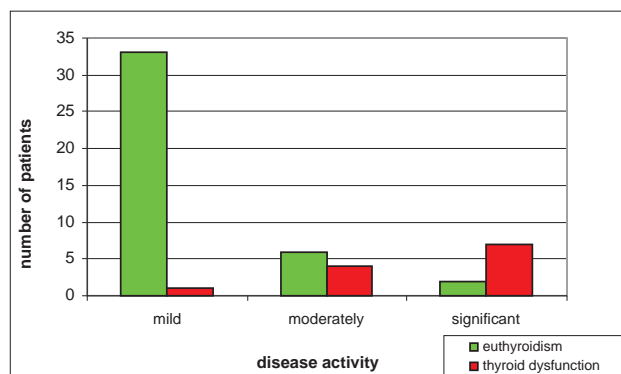
**Table 2.** SLE and RA patients according to age, duration of the disease and thyroid function.

patients	SLE		RA	
	mean age $\pm$ SD (years)	duration of the disease (years)	mean age $\pm$ SD (years)	duration of the disease (years)
euthyroid	45.17 $\pm$ 8.67	8.83 $\pm$ 3.76	52 $\pm$ 7.5	9.42 $\pm$ 6
thyroid dysfunction	37.75 $\pm$ 6.27	3.12 $\pm$ 2.48	60.6 $\pm$ 11.9	5.2 $\pm$ 3.32
subclinically hypothyroid	34.83 $\pm$ 9.3	1.75 $\pm$ 1	55.3 $\pm$ 9	6.7 $\pm$ 5
clinically hypothyroid	45.5 $\pm$ 4	0.75 $\pm$ 0.35	62	1

Subclinical hypothyroid SLE patients were younger than clinically hypothyroid SLE patients (34.83 vs 45.5 years, table 3) and the same was observed in the RA subgroup (55.3 vs 62 years). SLE lasted a significantly shorter period of time in patients with thyroid dysfunction compared to SLE patients with normal thyroid function (3.12 vs 8.83 years). It is also noted in this study that patients with normal thyroid function had significantly more benign forms of the disease ( $ECLAM \leq 2$ ), as opposed to the SLE patients with thyroid dysfunction who had moderately and clinically aggressive SLE ( $ECLAM > 2$  and  $ECLAM > 5$  respectively) (figure 1).

**Table 3.** Thyroid function in CTD patients and in the control group

Thyroid function	SLE	RA	SSc	SSy	CTD	control
euthyroidism (No.)	41	19	6	6	72	33
hypothyroidism (No.)	8	4	1	1	14	1
subclinically (No.)	6	3	1	1	11	1
clinically (No.)	2	1	0	0	3	0
hyperthyroidism (No.)	4	1	0	0	5	0
subclinically (No.)	2	1	0	0	3	0
clinically (No.)	2	0	0	0	2	0



**Figure 1.** Thyroid function according to SLE activity

**Serology**

Positive anti-TPO Abs were detected in 20/91 patients with CTD and in 12/53 SLE patients, which was a significantly higher rate than in the healthy subjects ( $p < 0.05$ ) (Table 4). Patients with RA, SSc and SSy had a higher prevalence of anti-TPO Abs when compared to the controls, but the difference was not statistically significant.

It was found that 9 of all CTD patients, 6/53 patients with SLE and 3/24 RA patients had positive anti-Tg Abs, which was higher than in the control group, but the difference was not statistically significant. SSc and SSy patients did not have positive antithyroid antibodies.

**Table 4.** Antithyroid antibodies in CTD patients

Antithyroid autoantibodies	SLE (No.)	RA (No.)	SSc (No.)	SSy (No.)	CTD (No.)	control (No.)
anti-TPO Abs	12	5	2	1	20	2
anti-Tg Abs	6	3	0	0	9	1

**DISCUSSION**

This study confirms previous reports that showed altered thyroid functions in patients with CTD. The appearance of ATD in patients occurred with greater frequency than in the control group. However, a higher prevalence of thyroid dysfunction in subjects studied here than Arnout et al (1) have found, could be explained by the fact that subclinical hypothyroidism was detected more often.

A number of studies have looked at the prevalence of thyroid disease in SLE. In this study a significantly greater number of patients had thyroid dysfunction as opposed to the subjects in the control group. The prevalence of hypothyroidism and hyperthyroidism was in accordance

with some studies (3, 13), whilst higher, compared to the others (11, 14). The prevalence of hypothyroidism was higher than the prevalence of hyperthyroidism which was in agreement with the other studies (3, 11, 13, 14).

Thyroid dysfunction found in RA patients was significantly higher than in the control group, and also higher than in the majority of reported studies (6, 12), excluding Caron et al. (5) who found thyroid dysfunction even in 33.8% of RA patients. The prevalence of hypothyroidism in this study was higher than hyperthyroidism and was in concordance with earlier studies (5, 6, 15).

Also, age of SLE and RA patients studied here positively correlated with clinical expression of the thyroid disease, as the subclinically hypothyroid patients were younger than patients with clinical hypothyroidism. The follow-up study of the Wickham survey (16) showed that clinical hypothyroidism rarely developed below the age of 45 and peaked around the age of 80. The results from this study are in agreement with the hypothesis of a slow universal progression of the autoimmune thyroiditis through the model of the „disease pyramid“ (17). This model suggests that patients progress from mild thyroiditis to clinical disease over time. One could assume that RA and particularly SLE accelerate further progress to ATD. Well -matched controlled clinical studies in which SLE and RA patients with subclinical hypothyroidism are followed up, could approve or disapprove this hypothesis.

These results showed that ATD developed in younger SLE patients in which SLE lasted shorter and was clinically more aggressive. This could indicate the existence of a genetic predisposition for „autoimmunity in general“ which would result in an earlier development of thyroid or other organ dysfunction in the course of systemic autoimmunity, especially if they are clinically aggressive (15).

The prevalence of subclinical hypothyroidism in SSc and SSy patients was similar to the results of some other, earlier performed studies (7-10, 18, 19), but occurred less often than in other studies, mainly performed with a higher number of patients (20, 21).

Positive anti-TPO Abs were detected in 20 of CTD patients, which was significantly higher than in the control group, but also higher than in the study of Arnout et al. (1). A significantly higher prevalence of anti-TPO Abs and a higher prevalence of anti-Tg Abs in SLE patients than in the control group were obtained and these results were in agreement with several studies (4, 13, 14, 22). SLE patients with thyroid dysfunction had higher prevalence of antithyroid antibodies (8/12) than patients with normal thyroid function, confirming the coexistence of the SLE and ATD. Half of SLE hypothyroid patients had anti-TPO Abs, which occurred more frequently than anti-Tg Abs and was in concordance with the Pyne and Isenberg study (14). SLE patients with antithyroid antibodies were younger than those without antibodies and the disease was more clinically aggressive. This was, however, different from other studies which showed higher prevalence of antithyroid antibodies in

elderly patients (4). A few studies, which were done in children with SLE, showed that younger patients often had aggressive forms of disease associated with other autoimmune phenomena (23). It is possible to assume that younger patients with active SLE and with positive serological findings will develop a subclinical form of the disease and afterwards clinical thyroid disease.

Anti-TPO Abs in 5 of RA patients were found, which was higher than in the control group and was slightly more prevalent than in the other studies (5, 6, 15). A higher prevalence of anti-TPO Abs in RA patients from this study (mean age was 54 years) is in accordance with Whickham's study (16) which showed increased prevalence of anti-TPO Abs with the age.

The prevalence of anti-TPO Abs in SSy patients under this study was higher than in the control group, but was lower than in other studies (18, 21). In the study of Foster et al. (19) they showed that 11.4% of the first degree relatives and 7.5% of the second degree relatives of SSy patients had thyroid dysfunction or positive serological findings. On the other hand, Coll et al. (24) published subclinical SSy in one third of patients with ATD. These observations suggest that there is a genetic predisposition for organ-specific autoimmune processes which could involve salivary as well as the thyroid gland, because of their similar functional characteristics and antigens.

The differences in the thyroid function and antithyroid autoantibodies in CTD patients, in the SLE, RA, SSy

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and SSc subgroups, obtained in this and herein discussed studies, could be explained by different number of subjects, the age of patients and duration of CTD, as well as disease activity. Because of that, all factors that could influence the appearance and course of autoimmune thyroid disease in patients with CTD need to be further analyzed.

This was the first study in the Serbian population that examined the prevalence of altered thyroid function and antithyroid autoantibodies in order to detect the presence of ATD in CTD patients, as well as in SLE, RA, primary SSy and progressive SSc subgroups. A statistically higher prevalence of thyroid disease in CTD was found, as well as in SLE and RA patients when compared with the age and sex matched controls. This is especially evident in SLE patients with clinically aggressive forms of disease. The presence of hyperthyroidism and particularly hypothyroidism in CTD patients and SLE subgroup is associated with a higher prevalence of antithyroid, predominantly anti-TPO Abs. According to these results, intermittent screening of thyroid function and antithyroid autoantibodies in patients with CTD could be recommended.

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