ORIGINAL ARTICLE

Prevalence of thyroid diseases and antithyroid antibodies in women with rheumatoid arthritis

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KEY WORDS

autoimmune thyroid disease (ATD), rheumatoid arthritis (RA), thyroid antibodies

ABSTRACT

INTRODUCTION Thyroid abnormal function and and/or autoimmune thyroid disease (ATD) are observed in 6% to 33.8% patients with rheumatoid arthritis (RA).

OBJECTIVES The aim of the study was to determine whether ATD is more prevalent in patients with RA compared to the control group involving age and sex-matched subjects without RA and whether these patients should be screened for thyroid disease.

PATIENTS AND METHODS In 100 patients with RA and 55 patients without RA (control group) hormonal thyroid function and antithyroid antibodies were assessed.

RESULTS ATD was more prevalent (16%) in patients with RA than in the control group (9%). The difference was no statistically significant. The RA patients with concomitant ATD had lower RA activity than non-ATD RA patients. Antithyreoglobulin (anti-TG) and antithyroid peroxidase (anti-TPO) antibodies were present in similar percentage of patients with RA (12% and 15%, respectively) and in the control group (9% and 18%, respectively). The most common thyroid dysfunction observed in both groups was subclinical hypothyroidism. An association between thyroid dysfunction and clinical symptoms suggestive of thyroid disease in RA patients was not demonstrated. In patients with RA low free triiodothyronine concentrations were significantly more common.

CONCLUSIONS A higher prevalence of ATD in female RA patients compared with controls indicates the need for screening not only of thyroid function, but also of the presence of anti-TPO antibodies as the ATD marker in RA patients. Their presence does not correlate with the occurrence of thyroid disorders in RA patients. Monitoring of thyroid function is of particular importance since as already shown the course of thyroid disease in RA patients is often asymptomatic.

INTRODUCTION A hormonal dysfunction and/or autoimmune thyroid disease (ATD) are present in 6% to 33.8% patients with rheumatoid arthritis (RA).[1-7] The concomitant presence of these diseases is more frequent in women than men.[3,6,8,9] Clinical manifestation of these diseases is often proceeded by presence of characteristic organ specific antibodies that might occur in serum even a few years before symptom onset and making a diagnosis.[10] However, it is not a reliable early symptom of the disease because the antibodies are also found in low concentrations in healthy individuals.

Apart from genetic background no other factors predisposing to the concomitant presence of thyroid diseases and RA have been established. Age, duration and activity of RA, the presence of rheumatoid factor and antinuclear antibodies have not been found to predispose to coexistence of these diseases.[2,3,5,6,8,11]

Because of asymptomatic course of ATD in the initial phase diagnosis might be difficult to be established. This induces the search of the factors that could identify individuals particularly prone to the development of these diseases.

Most thyreologists do not recommend routine population screening for thyroid diseases. It is thought that individuals from risk groups (of thyroid diseases development) should be screened i. e women with family history of thyroid diseases, with previous thyroid dysfunction, with symptoms suggestive of hyperthyroidism or hypothyroidism, with abnormalities in physical examination of the thyroid gland, type 1 diabetes and a history of other autoimmune diseases.[12]

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TABLE 1 Characteristics of females with RA

	RA (n = 100)
age (min., max.)	(21, 88)
mean (standard deviation)	56 (13)
family history of RA	
negative	77 (77%)
positive	23 (23%)
number of painful joints	
(min., max.)	(0, 28)
median (25%, 75%)	10 (7, 18)
number of swollen joints	
(min., max.)	(0, 14)
median (25%, 75%)	4 (2, 7)
rheumatoid factor	
(min., max.)	(12.5, 2460)
median (25%, 75%)	122 (29.5, 345)
rheumatoid factor >34	71 (71%)
methotrexate	81 (81%)
dosage mg/week	n = 81
(min., max.)	(7.5, 20)
median (25%, 75%)	12.5 (12.5, 15)
prednisone	
not taken	40 (40%)
up to 10 mg/d	53 (53%)
>10 mg/d	7 (7%)
DAS 28	
(min., max.)	(1.05, 8.11)
median (25%, 75%)	5.65 (4.86, 6.31)
DAS 28	
low (<3.2)	2 (2%)
moderate (3.2–5.1)	32 (32%)
high (>5.1)	66 (66%)
HAQ	n = 56
(min., max.)	(0.37, 3)
median (25%, 75%)	2.0 (1.5, 2.62)
HAQ >2	28 (50%)

Abbreviations: DAS 28 – Disease Activity Score, HAQ – Health Assessment Questionnaire, RA – rheumatoid arthritis

The purpose of the study was to determine whether ATD is more prevalent in patients with RA and whether these patients should be screened for thyroid diseases.

PATIENTS AND METHODS Two groups of women were studied. In the first group 100 women with RA were diagnosed on the basis of ACR criteria (American College of Rheumatology) from 1987.[13] Patients were recruited at random. Consecutive patients were admitted to the Clinical Department of Rheumatology of Rheumatology Institute in years 2001–2005. Only women were enrolled into the study because RA and ATD are more common in women. It allowed to obtain the study groups large enough to do the statistical analysis.

The control group involved 55 women without RA who volunteered to take part in the study.

In all the patients the following examinations were performed:

1 clinical examination i. e. medical history taking (including history regarding thyroid diseases, RA and its familial occurrence), physical examination with internal examination and musculoskeletal system assessment (28 joints assessment according to EULAR criteria), and evaluation of goiter and its grade according to World Health Organization. Disability was assessed on the basis of *Health Assessment Questionnaire (HAQ)*. Activity of RA was evaluated using the Disease Activity Score (DAS 28) with 4 parameters.

2 Laboratory tests used to evaluate RA activity: erythrocyte sedimentation rate, C-reactive protein (CRP); antinuclear antibodies (ANA) and tests of thyroid function and occurrence of autoimmune thyroid disease:

A thyroid-stimulating hormone (TSH), free triiodothyronine (fT_3), free thyroxine (fT_4) – their concentrations were determined using chemoiluminescence with the use of ELECYS 1010 analyzer (Roche Diagnostic). The reference values for TSH were 0.27–4.2 mIU/l, for fT_3 2.57–4.43 pg/ml and for fT_4 0.93–1.71 ng/dl.

B antithyreoglobulin (anti-TG) antibodies and antithyroid peroxidase (anti-TPO) antibodies were determined in the Department of Microbiology and Serology. The tests were performed usingan ELISA assay (HYCOR) and Biomedica solution. The reference values for anti-TG antibodies were <325 IU/ml and for anti-TPO <50 IU/ml.

3 Thyroid ultrasound was not routinely performed because of its limited availability. It was performed at the Radiology Unit, Institute of Rheumatology in 14 RA patients. There were no indications for thyroid biopsy in any of the study patients.

4 ATD diagnosis was made based on the presence of antithyroid antibodies (presence of anti-TPO antibodies was a prerequisite for the diagnosis) in patients with concomitant thyroid dysfunction and/or goiter. ATD was suspected based on the values of anti-TPO antibodies close to the limits of the reference range and positive anti-TG antibodies.

Statistical analysis In the statistical analysis the end point was the incidence of RA. In the patients with RA the endpoints were disease activity measured by DAS 28, functional disability assessed by HAQ score and the percentage of rheumatoid factor positive patients. Potential risk factors were: thyroid function, ATD, anti-TG, anti-TPO, TSH, fT_3. Statistical analysis of the results was carried out using multivariate logistic regression models. Backward stepwise elimination procedure was used to construct the final model. All independent variables retained in the model were statistically significant at $\alpha = 0.05$. The goodness of fit of the models was checked with Hosmer-Lemeshow test. The predictive value of the models was assessed with the use of the area under the ROC curve. In additional statistical analysis Kruskal-Wallis, Chi^2

TABLE 2 Prevalence of thyroid diseases in RA group and control group

	Control group n = 55	RA group n = 100
history of thyroid diseases	4 (7%)	25 (25%)
type of thyroid disease		12 (12%)
toxic nodular goiter	1(2%)	5 (5%)
non-toxic nodular goiter	2(4%)	2 (2%)
Graves's disease		6 (6%)
Hashimoto's disease	1(2%)	
duration of thyroid diseases	(0.5, 5)	
(min., max.)	2	(0.08, 40)
median (25%, 75%)		5 (3, 15)
goiter grade		
0	52 (95%)	85 (85%)
1	2 (4%)	9 (9%)
2	1 (2%)	5 (5%)
3	0	1 (1%)
thyroid function		
euthyreosis	51 (93%)	90 (90%)
subclinical hypothyroidism	3 (5%)	7 (7%)
subclinical hyperthyroidism	0	1 (1%)
hypothyroidism	1 (2%)	0
hyperthyroidism	0	2 (2%)
autoimmune thyroid disease		
none	50 (91%)	84 (84%)
diagnosed before hospitalization	1 (2%)	8 (8%)
diagnosed during hospitalization	3 (5%)	7 (7%)
suspicion	1 (2%)	1 (1%)
age (min., max.)	(19, 75)	(21, 88)
mean (standard deviation)	54 (12.2)	56 (13)
thyroid disease clinical symptoms		
no clinical symptoms	55 (100%)	79 (79%)
palpitation	0	21 (21%)

and Fisher tests were used and Spearman correlation coefficients were calculated when appropriate. In all the tests performed critical regions were two-sided at $\alpha = 0.05$ unless stated otherwise. Since the majority (81%) of the RA subjects was treated with methotrexate we did not examine the effect of treatment on the analyzed parameters. It has been assumed that the study group was homogenous with regard to the medication used.

RESULTS Both studygroups did not differ with regard to age. In 71% of patients with RA rheumatoid factor was detected. Positive family history of RA was observed in 23% of women with RA. Duration of RA was 0.5 to 49 years, mean 12.3 years.

All patients but one were actively treated for RA, i.e. 81 women were given methotrexate in the dose from 7.5 to 20 mg/week (median 12.5 mg), 3 patients in combination with cyclosporine and 1 in combination with sulphasalazine, 14 women were treated with sulphasalazine, 1 with leflunomide, 3 with azathioprine.

60% of the patients were treated with corticosteroids, and in most of them (53%) low dose was used (up to 10 mg when converted to prednisone) (TABLE 1).

The history of thyroid disease was reported by 25% of the RA patients and by 7% of the control patients. Toxic nodular goiter (12%) in the RA patients and nontoxic nodular goiter (4%) in the control group were the most common cases. Hashimoto disease was reported by 6 RA patients and by 1 patient from the control group, while Graves-Basedow disease was diagnosed in one RA patient.

Most patients from the study group did not manifest clinical symptoms suggestive of the thyroid disease. Palpitation was the only symptom in the RA patients. Goiter was present in both the RA patients and the control group, in 15% and 6% of them, respectively, mostly grade I goiter (WHO classification).

ATD was more prevalent in patients with RA compared to the control group (16 *vs* 9%). The difference was not statistically significant. ATD was diagnosed in 8% of women with RA before enrollment into the study and in further 8% the diagnosis was made while performing additional tests. Most RA patients (10% *vs* 6%) were diagnosed with ATD already during the course of RA.

Only 1 patient (2%) from the control group had a history of ATD. Subclinical hypothyroidism was the most common thyroid dysfunction in the ATD patients.

No significant differences were found in thyroid hormone status in both groups. The majority of the study group (90%) and control group (93%) subjects demonstrated normal thyroid function (euthyreosis). The most common thyroid dysfunction observed in both groups was subclinical hypothyroidism (5% *vs* 7%), with increased TSH and normal fT_4 levels. Hypothyroidism was found in 2% of the RA patients compared to none in the control group. An association between thyroid hormone dysfunction and clinical symptoms suggestive of thyroid disease in the RA patients was not demonstrated.

At the time of the study, 2 RA patients were undergoing treatment for thyroid diseases; 1 patient with Graves-Basedow's disease was treated with methimazole (10 mg/day) and 1 patient with Hashimoto's disease with L-thyroxine (100 μg/day). In the control group, 1 patient with Hashimoto's disease was treated with L-thyroxine (75 μg/day).

Comparison between both groups in respect of the presence of thyroid diseases and symptoms is presented in TABLE 2.

The most common ultrasound findings were nodules with features of a cyst and hetrogenous or hypoechoic parenchymal structure not suggestive of ATD; there were no indications for biopsy of the gland (TABLE 3).

In search for factors that may characterize and identifying the RA patients with and without concomitant ATD, both groups were compared. Compared to the non-ATD RA patients, the RA patients with concomitant ATD displayed lower

TABLE 3 Results of thyroid ultrasonography in RA patients

Thyroid ultrasonography	RA (n = 14)
hypoechogenicity	2 (2%)
erogenous echogenicity	5 (5%)
increased perfusion	3 (3%)
nodules (cysts)	10 (10%)

TABLE 4 Multivariate analysis of the impact of parameters presented in the table on high DAS 28 scores in RA patients (n = 73)

DAS 28 ≥5.1 (n = 48)	p
goiter grade 1–3 vs. 0	>0.1
thyroid dysfunction vs. euthyreosis	>0.1
autoimmune thyroid disease present vs. none	>0.1
supernormal TSH vs. other	>0.1
subnormal fT_3 vs. other	>0.1
TG >325 vs. other	>0.1
TPO > 50 vs. other	>0.1

Abbreviations: fT_3 – free triiodothyronine, OR – odds ratio, TG – thyreoglobulin, TPO – thyroid peroxidase, TSH – thyroid-stimulating hormone

RA activity assessed using the DAS 28 and serum CRP. Thyroid functional disorders were more common in the RA patients with concomitant ATD than in the non-ATD patients (Fisher's exact test, p = 0.009).

Anti-TG antibodies and anti-TPO antibodies were present in similar percentage of patients with RA (12% and 15%, respectively) and their prevalence in the control group (9% and 18%, respectively) was similar.

Anti TPO antibodies were significantly frequent in patients with TSH >4.2 (p <0.001) and TSH >2 (p = 0.003). No correlations were found between presence of anti TPO antibodies and thyroid dysfunction in patients with RA. Such correlation was found in the control group. This dysfunction cases involved hypothyroidism and subclinical hypothyroidism (p = 0.016).

In patients with RA reduced fT_3 concentrations were significantly more common.

In multivariate analysis there has been no evidence that high RA activity correlated with goitre grade, thyroid function, the presence of autoimmune thyroid disease or antinuclear antibodies (TABLE 4). However, patients with high RA activity were characterized by high disability index HAQ >2 (OR = 7.7, p = 0.006).

Thyroid dysfunction is adversely associated with positive rheumatoid factor (p = 0.012) (in patients with thyroid dysfunction rheumatoid factor is less prevalent).

DISCUSSION The study showed higher prevalence of ATD in the RA female patients, although the difference was not statistically significant. It should, however, be stressed that prevalence of ATD in the control group (9%) was significantly higher than in the Polish population, where Hashimoto's disease with hypothyroidism afflicts 0.4% of the whole population, and Graves-Basedow's disease 0.26% of females.[14] The result was probably influenced by a relatively small number of subjects in the control group.

Monitoring of anti-TPO antibodies and thyroid hormone function in female RA patients could reveal subjects with the asymptomatic course of ATD. In half of female RA patients with concomitant ATD, the ATD course was asymptomatic, and the diagnosis was made accidentally. Of note, as ATD was clinically silent also in patients with thyroid dysfunction diagnosed during the study.

It is worth noting that patients with RA and concomitant ATD have lower activity of RA in comparison to patients with RA without this thyroid disease. This observation is difficult to explain as so far no relationship between thyroid diseases and RA activity was found.[2,3,6,8,11] Higher disability index HAQ was reported in patients with RA with concomitant thyroid diseases[9] what has not been confirmed in the study population with RA.

Anti-TPO antibodies are frequent in Hashimoto disease (up to 95% of the patients) and Graves-Basedow disease (up to 80% of the patients).[15]

The prevalence of anti-TG and anti-TPO in the current study population was similar and was 12% and 15%, respectively. It was not statistically significantly different from their prevalence in the control group (9% and 18%). Our results were similar to values reported earlier in Polish populations of patients with RA,[16] as well as the data from European literature.[2,3,6,8,9,17,18]

While analyzing the results it should be emphasized and taken into consideration that they were conducted in patients with a fairly long mean duration of RA (12.3 years) treated with immunosuppressive agents. They might differ from the results of the analysis of patients with early RA who have not been treated so far. It was emphasized by Italian authors investigating such the population. The percentage of antithyroid antibodies reached 30% and was significantly higher from that observed in other Italian studies.[18,19]

The current study showed that occurrence of anti-TPO antibodies is more frequent with TSH not only above the upper reference limit, but also within this range. The presence of anti-TPO in patients with normal thyroid function might be of no clinical significance. However, simultaneously it might be the marker that precedes and heralds the development of the disease.[10,20-22] It is the similar situation as with IgM class rheumatoid factor or anticitrullinated antibodies (anti-CCP) present in serum of healthy people 0.1 to 13.8 years before RA development.[23] In the study population we observed the presence of anti-TG and/or anti-TPO antibodies and no other abnormalities in thyroid parameters (assessed in our study) in 6 patients with RA and in 4 women from the control group. These

patients require follow-up and TSH monitoring every 3–5 years.[24]

In patients with RA thyroid dysfunction is even three times more frequent than in the general population.[5,6,8,11,16,17,25] In our study the thyroid dysfunction was observed slightly more often in patients with RA (10%) than in the control group (7%).

Attention should be drawn to the fact that only 3 of 10 studied patients with concomitant RA and thyroid dysfunction had clinical manifestations suggesting the thyroid disease. The asymptomatic or mildly symptomatic clinical course of thyroid diseases in RA patients may be masked by underlying disease, which symptoms predominate in clinical manifestation, posing hazards of late diagnosis and treatment, what has also been noticed previously.[3,8,24]

The most common thyroid dysfunction in the study population was subclinical hypothyroidism, which according to the literature is present in 9.4%–21% of patients with RA.[11,18,19,26] It was shown that it is the risk factor of overt hypothyroidism development, which is additionally favored by age, female sex and anti-TPO antibodies.[24] Moreover, subclinical hypothyroidism increases the risk of hypercholesterolemia development and early atherosclerosis as well as insulin-resistance.[10,26-29] There are no reliable evidence that early treatment with L-thyroxine in patients with subclinical hypothyroidism prevents the development of hyperlipidemia and atherosclerosis.[30,31] Therefore, those patients should in particular receive prophylaxis of atherosclerosis.

Female RA patients manifest low fT_3 syndrome, which is probably a result of disorder in peripheral conversion of thyroxine into triiodotironine due to the chronic inflammatory process.

In conclusion, a higher prevalence of ATD in female RA patients in comparison with controls indicates the need for screening not only of thyroid hormone function, but also of the presence of anti-TPO antibodies as the ATD marker in RA patients. Their presence does not correlate with the occurrence of thyroid hormone functional disorders in RA patients. Monitoring of thyroid function is of special importance since as already shown the course of thyroid disease in RA patients is often asymptomatic.

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