

Hypothyroidism and autoimmune thyroid disorders in rheumatoid arthritis: relationship with disease activity

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Abstract

Background and aims: Thyroid function abnormalities and thyroid autoantibodies have previously been described in rheumatoid arthritis (RA) with limited data. In some studies, a relationship was found between thyroid autoantibodies and RA disease activity. However, there are not strong studies in the literature indicating the relationship between thyroid diseases and RA. The aim of this study was to determine the frequency of hypothyroidism and to investigate the relationship between thyroid hormone levels, autoantibodies and disease activity in patients with rheumatoid arthritis (RA).

Methods: 1017 patients with the diagnosis of RA were recruited. This observational study was conducted between January 2014 and July 2015. Demographic variables were recorded. Anti-nuclear antibodies (ANA), anti-cyclic citrullinated peptide antibody (anti-CCP), Rheumatoid Factor (RF), C reactive protein (CRP), Erythrocyte Sedimentation Rate (ESR), thyroid stimulating hormone (TSH), triiodothyronine (T3), thyroxine (T4), anti-microsomal antibody (anti-TPO) and anti-thyroglobulin antibody (anti-TG) were determined. Visual analog score and Disease Activity Score 28 (DAS-28) ESR and DAS-28 CRP were recorded. The relationship between thyroid hormone levels and thyroid antibodies and disease activity parameters were determined.

Results: 98 (9,7%) patients had hypothyroidism and 61 (6%) patients had hyperthyroidism. 210 (20,7%) patients with RA was positive for TPOAb and 165 (16,3%) for anti-TG. Positive correlation was detected between anti-TPO positivity and anti-CCP levels ($p:0.005$, $r:0,274$). In anti-TG antibody positive patients, there was a significant positive correlation of thyroid hormone levels with CRP and DAS 28-CRP ($p:0.01$, $r:0,120$; $p:0.01$, $r:0,169$).

Conclusion: Thyroid autoantibodies were found to be positive in 16-21% of patients with RA. Though hypothyroidism is not very frequent in RA patients, autoimmune thyroid disease is quite common, which may be related to disease activity.

Key words: autoimmune thyroid disease, hypothyroidism, rheumatoid arthritis, autoantibodies, Disease Activity Score

What is new? What is important?

- Thyroid dysfunction especially hypothyroidism is common in patients with RA.
- 20,7% patients with RA was positive for TPOAb and 16,3% for anti-TG.
- There was a significant positive correlation of thyroid hormone levels with CRP and DAS 28-CRP in anti-TG antibody positive patients.
- RA activity may be associated with the presence of thyroid autoantibodies.
- Patients with RA should be followed carefully in terms of thyroid disease and thyroid function tests should be checked at regular intervals.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic, inflammatory disease affecting approximately 1% of the population and is the most common

inflammatory joint disease of systemic autoimmune diseases. Although the etiopathogenesis is not fully understood, multifactorial (environmental, genetic, etc.) causes are thought to play a role in the etiology of RA, as in many of the autoimmune

diseases. It is most common in the fourth and fifth decades, and occurs in 80% of patients between the ages of 35 and 40 [1].

Autoimmune diseases are observed more and more frequently all over the world. The most frequently affected organ among autoimmune diseases is the thyroid. Autoimmune thyroid diseases (ATD) are organ-specific autoimmune disorders characterized by the presence of antithyroid antibodies such as thyroglobulin, thyroid stimulating hormone receptor and anti-microsomal antibody. In the presence of appropriate environmental factors, these diseases may develop in genetically susceptible individuals [2].

Thyroid function abnormalities and thyroid autoantibodies have previously been described in rheumatoid arthritis with limited data. A hormonal dysfunction and/or autoimmune thyroid disease (ATD) were present in 6% to 33,8% patients with RA. Positivity for the thyroid autoantibodies has been detected in 11% of the patients with RA, ranging from 2%–32% in different case series [3].

It is known that autoimmune diseases can occur together, the most common ATD has been reported as subclinical hypothyroidism, clinical hypothyroidism and hyperthyroidism in the literature. In the study in 11782 RA patients of Hussein *et al.*, the frequency thyroid function disorder was found to be 18,33%, hypothyroidism 16%, and hyperthyroidism 2,33% [4]. Apart from genetic background no other factors predisposing to the concomitant presence of thyroid diseases and RA have been established [5]. 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. 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.

In some studies, a relationship was found between thyroid autoantibodies and RA disease activity. However, there are not strong studies in the literature indicating the relationship between thyroid diseases and RA. The aim of this study was to evaluate the frequency of thyroid diseases in RA and determine the relationship between ATD and disease parameters.

MATERIAL AND METHODS

Patients who submitted to the rheumatology outpatient clinic and department of Physical Medicine and Rehabilitation and diagnosed with

RA according to the RA 2010 ACR/EULAR classification criteria were included in our study. This observational study was conducted between January 2014 and July 2015. The total number of patients was 1107, and 140 patients were excluded because they did not meet the study criteria. Inclusion criteria in the study were follow-up and treatment with the diagnosis of RA between 2013 and 2015, being older than 18 years of age, and coming to routine controls. Exclusion criteria from the study were being pregnant and lactating woman, to be under the age of 18 and diagnosed with thyroid disease, using thyroid medication and having a history of thyroid surgery with or without using thyroid medication. Before the study was conducted, ethical approval was obtained from the ethics review board with the number 0504/4198. All procedures performed in studies involving human were in accordance with the ethical standards of the institutional research committee (Ankara Training and Research Ethical Committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Informed consent was not obtained since the study was conducted with retrospective patient data.

The demographic variables including age, gender, disease duration, comorbid diseases and treatments were determined from the patient follow-up files. DMARDs (Disease-modifying antirheumatic drugs, steroid, nonsteroidal anti-inflammatories drugs (NSAIDs), biological agents and other drugs used by the patients were recorded. Furthermore dose of methotrexate was recorded. Patient global assessment of pain and general health was measured using Visual analog score (VAS). Number of swollen joint count and tender joint count were recorded. The thyroid hormone levels and antithyroid antibodies comprising anti-TG antibodies, thyroperoxidase enzyme antibodies (TPOAb) were evaluated in all patients. Hypothyroidism was defined as a measured TSH level greater 5,33 mIU/L and hyperthyroidism was defined as a measured TSH level less than 0,38 mIU/L. Disease activity markers including DAS 28, ESR, CRP and pain levels by VAS a likert-type scale was used to measure pain intensity with a score ranging from 0 (no pain) to 10 (most severe pain) were recorded. The relationship between thyroid hormone levels and thyroid antibodies and disease activity parameters were determined.

The normal values of the central biochemistry laboratory of our hospital; 0.38–5.33 mIU/L for TSH, 0.61–1.12 ng/dL for T4, 2.3–4.2 pg/ml for T3, 0–9 U/mL for anti-TPO, for anti-g It was accepted

as 0–4 U/mL, 0–8 mg/L for CRP, 0–20 mm/hour for ESR, 0–20 IU/ml for Rheumatoid Factor (RF), <20 negative, ≥ 20 positive for anti-CCP

DAS-28 index was used to detect disease activity. Patients were asked to give a score between 0 and 100 to evaluate their own condition. The DAS-28 index was calculated using a fixed formula, using the number of swollen and tender joints, CRP/ESR, and the numbers given by the patients to indicate their general condition. RA was evaluated as high disease activity DAS28 > 5,1, moderate disease activity DAS28 $\geq 3, 2$ to $\leq 5,1$, low disease activity >2,6 to <3,2, <2,6 remission [6].

STATISTICAL ANALYSIS

Statistical evaluation IBM SPSS 20. 0 (IBM Corp., Armonk, NY, USA) package done with the program. Fitness to normal distribution Kolmogorov-Smirnov and Shapiro-Wilk evaluated with tests. Numerical variables were mean $\pm$ standard deviation and median (25–75th percentile), and

categorical variables were given as frequency (percentage). Between groups independent sample t-test for numerical variables with difference normal distribution, with Mann-Whitney U test for non-normally distributed numerical variables determined. Normal distribution assumption in the analysis of relationships between variables not available, Spearman correlation analysis was used. between categorical variables relationships were evaluated with Chi-square analysis. $P < 0.05$ in testing of two-way hypotheses was considered sufficient for statistical significance.

RESULTS

The demographic variables of this research are shown in Table 1. The mean age of the patients was 55.14 ± 13.68 (15–90 years). Most of the patients were female, with 804 (79.05%) female and 213 (20.95%) male (Table 1).

Table 1

Characteristics of patients affected with RA

Characteristics	Patients with RA
Number of patients	1017
Age, mean $\pm$ SD (range), years	55,14 $\pm$ 13,68 (15–90)
Female/male, n (%)	3,77 (804/213)
Disease duration, mean $\pm$ SD (range), years	11,5 $\pm$ 9,17 (20–41)
ESR, mean $\pm$ SD, mm/1st hour	23,2818 $\pm$ 14,897
CRP, mean $\pm$ SD, mg/dl	1,1150 $\pm$ 1,719
Rheumatoid factor, n (%)	570(56)
Anti-CCP, n (%)	522(51,4)
Antinuclear antibodies, n (%)	222(21,9)
Tender joint count, mean $\pm$ SD	1,0545 $\pm$ 2,0311
Swollen joint count, mean $\pm$ SD	0,0091 $\pm$ 0,09535
VAS, mean $\pm$ SD	27,73 $\pm$ 27,17
DAS28-ESR, mean $\pm$ SD	2,7232 $\pm$ 0,7733
DAS28-CRP, mean $\pm$ SD	2,3360 $\pm$ 10,17
<u>Medications</u>	
NSAIDs, n (%)	749(%73,63)
Prednisone, n(%)	342(% 33,63)
Methotrexate, n (%)	665(%65,45)
Other DMARDs, n (%)	305 (%30)

RA: rheumatoid arthritis, SD: standard deviation, ESR: erythrocyte sedimentation rate, CRP: C reactive protein anti-CCP: anti-cyclic citrullinated peptide antibody, VAS: Visual analog score, DAS: Disease Activity Score, NSAIDs: steroid, nonsteroidal anti-inflammatory drugs, DMARDs: Disease-modifying antirheumatic drugs

During the course of the study we evaluated all clinical variables and biomarkers, including ESR ($23,2818 \pm 14,897$ mm/1st hour), CRP ($1,1150 \pm 1,719$ mg/dl) and number of swollen joint count ($0,0091 \pm 0,09535$), tender joint count ($1,0545 \pm 2,0311$). Distribution of the number of patients according to autoantibodies; RF in 56% (570), anti-CCP in 51,4% (522), Anti-nuclear antibodies (ANA) in 21,9% (222) was positive (Table 1).

All patients but one were actively treated for RA, 49 patients (%73,63) were given NSAIDs 665 (%65,45) patients were given methotrexate in the dose from 7,5 to 20 mg/week (median 12,5 mg), 305 patients in combination with other DMARDs, 33,3% 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).

98 (%9,7) patients had hypothyroidism and 61 (%6) patients had hyperthyroidism. 210 (20,7%) patients with RA was positive for TPOAb and 165 (16,3%) for anti-TG (Table 2).

Among the 210 TPOAb positive patients, 144 (69%) were ANA positive, 168(81%) had anti-CCP antibodies and 137(65,4%) RF. Furthermore, among 165 anti-TG positive patients, 123 (75%) had ANA, 143(87%) anti-CCP antibodies and 113

(69%) RF. There was no statistically significant difference in terms of auto-antibodies between the group. Of 210 patients who were TPOAb positive; 156 (74.28%) were using NSAIDs, 72 (34.28%) were using Prednisone, 140 (66.66%) were using Methotrexate and 62 (29.52%) were using Other DMARDs. Furthermore, of 165 patients who were TPOAb positive; 123 (%75) were using NSAIDs, 57 (%34,54) were using Prednisone, 108 (%65,45) were using Methotrexate and 50 (%30,30) were using Other DMARDs. There was no statistically significant difference in terms of drug usement between the group (Table 3).

Between anti-TPO positivity, DAS-28-ESR, DAS-28-CRP, ESR, CRP, RF and ANA levels no correlation was observed. Positive correlation was detected between anti-TPO positivity and anti-CCP levels ($p:0.005$, $r:0,274$). Anti-CCP titers appeared to be high in the presence of anti-TPO. In anti-TG antibody positive patients, there was a significant positive correlation of thyroid hormone levels with CRP and DAS 28CRP ($p:0.01$, $r:0,120$; $p:0.01$, $r:0,169$) (Table 4). Between anti-TPO and anti-TG antibody positivity and drug usement no correlation was observed (Table 5).

Table 2

Prevalence Hypothyroidism and Autoimmune Thyroid Disorders in RA

TSH, mean $\pm$ SD, μ IU/ml	2,0721 $\pm$ 2,540
T3, mean $\pm$ SD, pg/ml	2,8732 $\pm$ 0,474
T4, mean $\pm$ SD, ng/ml	1,1348 $\pm$ 0,2639
Hypothyroidism (TSH> 5,33 μ IU/ml), n (%)	98 (%9,7)
Hyperthyroidism (TSH< 0,38 μ IU/ml), n (%)	61 (%6)
Anti-TPO, mean $\pm$ SD, U/ml	84,53 $\pm$ 239
Anti-TG, mean $\pm$ SD, U/ml	41,77 $\pm$ 127,9
Anti-TPO+, (>9 U/ml), n (%)	210(%20,7)
Anti-TG +, (>9 U/ml), n (%)	165(%16,3)

RA: rheumatoid arthirits, SD: standard deviation, TSH: thyroid stimulating hormone, T3: triiodothyronine, T4: thyroxine, anti-TPO: anti-microsomal antibody, anti-TG: thyroglobulin antibody

Table 3

RF, anti-CCP antibodies and ANA positivity frequency in patients and drug usement with RA positive for thyroid autoantibodies

	Anti-TPO + (n:210)	Anti-TG + (n:165)	p
RF +	137(65,4%)	113 (69%)	0,26
Anti-CCP +	168(81%)	143(87%)	0,33
ANA +	144 (69%)	123 (75%)	1,23
NSAIDs+	156(%74,28)	123(%75)	1,22
Prednisone	72(%34,28)	57(%34,54)	1,33
Methotrexate	140(%66,66)	108(%65,45)	1,29
Other DMARDs,	62(%29,52)	50(%30,30)	1,3

RF: Rheumatoid Factor, anti-CCP: anti-cyclic citrullinated peptide antibody, ANA: Anti-nuclear antibodies, RA: rheumatoid arthritits, anti-TPO: anti-microsomal antibody, Anti-TG: thyroglobulin antibody, NSAIDs: streoid, nonsteroidal anti-inflammatories drugs, DMARDs: Disease-modifying antirheumatic drugs

Table 4

The correlation of the presence of thyroid autoantibodies and disease parameters

	DAS28-ESR	DAS28-CRP	ESR	CRP	RF	Anti-CCP	ANA
	p/r	p/r	p/r	p/r	p/r	p/r	p/r
Anti-TPO(+)	0.347/0,104	0.111/0,100	0.186/0,69	0.436/0,293	0.072/0,119	0.005/0,274	0,105/ 0,20
Anti-TG (+)	0.538/0,129	0.01/0,169	0.321/0,20	0.01/0,120	0.556/0,148	0.106/0,322	0,112/ 0,110

DAS: Disease Activiy Score, ESR: erythrocyte sedimentation rate, CRP: C reactive protein, RF: Rheumatoid Factor, anti-CCP: anti-cyclic citrulli-nated peptide antibody, ANA: Anti-nuclear antibodies, anti-TPO: anti-microsomal antibody, Anti-TG: thyroglobulin antibody

Table 5

The correlation of the presence of thyroid autoantibodies and drug usement

	NSAIDs	Prednisone	Methotrexate	Other DMARDs,
	p/r	p/r	p/r	p/r
Anti-TPO(+)	0.147/0,28	0.121/0,8	0.192/0,69	0.082/0,31
Anti-TG (+)	0.321/0,27	0.073/0,169	0.231/0,3	0.105/0,32

Anti-TPO: anti-microsomal antibody, anti-TG: thyroglobulin antibody, NSAIDs: streoid, nonsteroidal anti-inflammatories drugs, DMARDs: Disease-modifying antirheumatic drugs

DISCUSSION

The findings of our study showed that thyroid dysfunction especially hypothyroidism is common in patients with RA. 20,7% patients with RA was positive for TPOAb and 16.3% for anti-TG. In anti-TG antibody positive patients, there was a significant positive correlation of thyroid hormone levels with CRP and DAS 28-CRP.

RA is a chronic autoimmune disease that is characterized by destruction of synovial joints, leading to severe disability and early mortality.

It affects approximately 0.5–1% of the society. The prevalence of RA for Turkey was reported as 0.45% in the study of Akar et al [7]. Autoimmune origin and non- autoimmune origin thyroidal dysfunction (TD) in RA has been reported with a frequency of 6–34%. The prevalence of TD in the presence of thyroid autoantibodies may increase up to 38%. This ratio to the general population It is significantly higher (2–3 times) compared to the others [8]. The reason for this is the common factor in the pathogenesis of these diseases. It is thought to be an autoimmune mechanism. In addition after anti-TNF therapy improvement, in hypothyroidism

in patients with RA; cytokines may be proof that can play pathogenetic role in the development of TD [9]. In many studies, the rate of anti-thyroid antibodies and thyroid dysfunction in RA patients was found to be significantly higher than in the normal population [8]. However, the exact pathological mechanisms are still unclear [10].

In the general population, the prevalence of ATD in women varies between 5–15% and 1–5% in men [10]. In our study, the prevalence of ATD in RA patients was found to be 12.4% in women and 3.8 % in men. Similar to literature data, it can be thought that female patients are at higher risk than males in the development of this disease. In previous studies, the frequency of ATD in RA patients was found to be significantly higher in women. Roldán *et al.* reported that 81.3% (n:650) of 800 patients with RA in Colombia were female [10]. In our study, 79.05% (n: 804) of our patients with RA and 88.2% (n: 96) of those with autoimmune thyroid disease were women.

There are many studies reporting an increased frequency of thyroid autoantibodies in RA. In a study conducted by Yavaşoğlu *et al.*, anti-TPO positivity was 15.9% and anti-TG positivity was 12% in 82 newly diagnosed RA patients [11]. In another study of patients with RA and their relatives, thyroid disease was detected in 6% of the patients, while TPO antibodies were found in 5% of men and 15% of women [12]. In a series of 101 patients with RA in Greece, TPO antibodies were detected in 12.9% of the patients and similar findings were found in 2 other studies [13–15]. In a study by Gonçalves *et al.* in Brazil in 2006–2007, TPO antibodies were found in 15.27% and Tg antibodies in 12.5% in 72 patients with RA. In a recent study conducted in the same country, Tg and/or TPO antibodies were found in 32% of 25 patients with RA. [16, 17]. These data support the association between RA and ATD. The prevalence of thyroid antibodies generally ranges from 6–31% for anti-Tg, 5–37% for anti-TPO, and 10.4–32% for the presence of either [18–22]. Similar to other studies, the frequency of anti-TPO (20.7%, n: 210) and anti-TG (16.3%, n: 165) were high in 1107 patients with RA. Using different normal reference intervals and different methods for thyroid autoantibodies; this may explain the high prevalence variability.

The number of studies showing the change in RA severity by evaluating the link between ATD and RA is insufficient. No correlation was found between anti-CCP and thyroid autoantibodies,

which was examined in 754 patients in England in 2011 by Peter J Charles *et al.* [23]. Cojocaru-Goie *et al.* found a significant relationship between thyroid autoantibodies and anti-CCP antibodies [24]. In the 637 disease cohort of Amir *et al.*, in the presence of thyroid dysfunction and especially in hypothyroidism, the treatment response of RA patients is low and the disease has been shown to have high activity [25]. In our study, significant relationship was found between anti-CCP and anti-TPO. More studies are needed to demonstrate the relationship between thyroid autoantibodies and RA antibodies.

In a study conducted 75 RA patients hospitalized in Poland in 2013 by Arkadiusz Koszarny *et al.*; statistical significance was found between anti-TPO and DAS 28 score, anti-TG and ESR, and anti-TG and CRP levels. In this study, a significantly higher mean DAS 28 score was found in anti-TPO positive and Anti-TG positive patients compared to anti-TPO and anti-TG negative patients [26]. In our study, DAS 28 CRP, CRP scores were found to be statistically high in patients with ATD compared to those without. These results suggest that RA activity may be associated with the presence of thyroid autoantibodies.

There was no difference was found in the use of DMARDs and prednisolone between anti-TPO and anti-TG patients and negative patients in a study by Koszarny *et al.* [26]. Amir *et al.* reported that although their study showed that thyroid disorders in RA patients negatively affected the response to treatment and increased disease activity, it had no effect on drug usement [25]. Similarly we found that between anti-TPO and anti-TG antibody positivity and drug usement no correlation was observed.

The incidence of hypothyroidism is reported to be between 2.5% and 11% in patients with RA [27, 28]. In the study of Seyit Uyar *et al.* frequency of subclinical hypothyroidism was found to be 5.6% in 54 RA patient [29]. The rate of 9.7% (n:98) we found in our study is similar to other studies. Our study showed that hypothyroidism is common thyroid disorder associated with RA, similar to other studies [19, 21, 28, 30].

There were several limitations in this study. Important predictors such as occupational risk factors, smoking, exposure to environmental radiation and family history were not investigated. Although the number of patients was high, this was a single-center study.

CONCLUSION

As a result the coexistence of RA and ATD is common, and therefore, patients with RA should be followed carefully in terms of thyroid disease

and thyroid function tests should be checked at regular intervals. Therefore, thyroid dysfunction effects can be avoided with RA follow-up and treatment.

Introducere: Anomaliile funcției tiroidiene și autoanticorpilor tiroidieni au fost descrise anterior în poliartrita reumatoidă (AR) dar datele au fost limitate. În unele studii, a fost găsită o relație între autoanticorpilor tiroidieni și activitatea bolii. Cu toate acestea, nu există studii pe esantioane mari în literatură care să indice relația dintre bolile tiroidiene și AR. Scopul acestui studiu a fost de a determina frecvența hipotiroidismului și de a investiga relația dintre nivelul hormonilor tiroidieni, autoanticorpi și activitatea bolii la pacienții cu poliartrită reumatoidă (AR).

Metode: Au fost recrutați 1017 pacienți cu diagnostic de AR. Acest studiu observațional a fost realizat în perioada ianuarie 2014 – iulie 2015. Au fost înregistrate variabile demografice. Anticorpi antinucleari (ANA), anticorpi peptidici anti-ciclici (anti-CCP), factor reumatoid (RF), proteină C reactivă (CRP), rata de sedimentare a eritrocitelor (ESR), hormon de stimulare a tiroidei (TSH), triiodotironina S-au determinat (T3), tiroxina (T4), anticorpii anti-microzomal (anti-TPO) și anticorpii anti-tiroglobulină (anti-TG). S-au înregistrat scorul vizual analog și Scorul de activitate al bolii 28 (DAS-28) ESR și DAS-28 CRP. S-a determinat relația dintre nivelul hormonilor tiroidieni și anticorpii tiroidieni și parametrii activității bolii.

Rezultate: 98 (9,7%) dintre pacienți au avut hipotiroidism și 61 (6%) dintre pacienți au avut hipertiroidism. 210 (20,7%) pacienți cu RA au fost pozitivi pentru TPOAb și 165 (16,3%) pentru anti-TG. A fost detectată o corelație pozitivă între pozitivitatea anti-TPO și nivelurile anti-CCP ($p: 0,005$, $r: 0,274$). La pacienții cu anticorpi anti-TG pozitivi, a existat o corelație pozitivă semnificativă a nivelurilor de hormoni tiroidieni cu CRP și DAS 28-CRP ($p:0,01$, $r:0,120$; $p:0,01$, $r:0,169$).

Concluzie: Autoanticorpilor tiroidieni s-au dovedit a fi pozitivi la 16–21% dintre pacienții cu AR. Deși hipotiroidismul nu este foarte frecvent la pacienții cu RA, boala tiroidiană autoimună este destul de frecventă, care poate fi legată de activitatea bolii.

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