Autoimmune thyroid disorders in seropositive versus seronegative rheumatoid arthritis

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Background

Autoimmune diseases are chronic conditions initiated by the loss of immunological tolerance to self-antigens; they represent a heterogeneous group of disorders that afflict specific target organs or multiple organ systems. Autoimmune thyroid disease (AITD) is a common organ-specific autoimmune disorder affecting mostly middle-aged women. AITD is a term that includes various clinical forms of autoimmune thyroiditis; among these diseases, Hashimoto's thyroiditis and Graves' disease are the two most common types and share many features immunologically. Rheumatoid arthritis (RA) is a chronic inflammatory disease that leads to severe disability and premature mortality. Given the same pathogenic mechanisms, autoimmune diseases tend to cluster together, and hence this study was designed to investigate the relationship between AITD and RA, particularly seropositive versus seronegative subtypes.

Patients and methods

The study included 70 patients with evidence of RA. Their diagnosis was based on the 2010 American College of Rheumatology (ACR)-EULAR classification criteria, and they were subclassified into two groups: group I, comprising 35 patients with seropositive RA (positive to one or both seromarkers), and group II, comprising 35 patients with seronegative RA (negative to both seromarkers). Twenty healthy age-matched and sex-matched controls constituted group III. All of the studied participants underwent detailed history-taking and physical examination, focusing on RA duration of illness, clinical features suggestive of thyroid dysfunction, and disease activity score (DAS28). We determined the complete blood count, erythrocyte sedimentation rate, C-reactive protein, urea, creatinine, alanine aminotransferase, aspartate aminotransferase, thyroid stimulating hormone (TSH), serum total T3 (TT3), serum total T4 (TT4), rheumatoid factor (RF), anti-cyclic citrullinated peptide (anti-CCP), anti-thyroid peroxidase (anti-TPO), thyroglobulin Ab, and TSH receptor antibody (TRAb) levels, and also performed a neck ultrasound.

Results

It was found that erythrocyte sedimentation rate, C-reactive protein, RF, and anti-CCP were significantly higher in RA patients versus controls, particularly in seropositive versus seronegative patients. No significant difference was found between the studied groups as regards TSH, T3, and T4 levels; however, hypothyroidism was found to be more common than hyperthyroidism in RA patients (29 vs. 3% in group I and 9% in group II). Anti-TPO and antithyroglobulin were significantly higher in RA patients versus controls ($P < 0.001$) and specifically in seropositive (1301.9 ± 1716.0 and 1750.0 ± 1866.2, respectively) versus seronegative patients (799.4 ± 1597.7 and 898.1± 988.11, respectively). TRAbs were detectable in a small subset of RA patients (6% regardless of the serostatus) with significant difference between patients and controls ($P = 0.006$). Ultrasonographic features of thyroiditis were significantly evident in RA patients versus controls ($P = 0.001$). A positive correlation was found between RA autoantibodies (RF and anti-CCP) and thyroid autoantibodies (mainly anti-TPO and TRAbs) ($P = 0.007$, 0.012, 0.004, and 0.035, respectively).

Conclusion

Thyroid dysfunction and AITD are common in RA patients, with hypothyroidism being the most common disorder, which is prevalent in 29% of patients regardless of their serostatus. This association was independent of disease activity assessed by DAS28. Increased incidence of thyroid autoimmunity was seen in seropositive RA versus seronegative RA patients, as evidenced by higher levels of thyroid autoimmune markers in the former. TRAbs were detectable in a small subset of patients with RA.

Keywords:
autoimmune thyroid disorders, rheumatoid arthritis, seropositive, seronegative, thyroid peroxidase antibodies, TSH receptor antibodies

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Introduction

Autoimmune diseases (ADs) are chronic conditions initiated by the loss of immunological tolerance to self-antigens; they represent a heterogeneous group of disorders that afflict specific target organs or multiple organ systems. The chronic nature of these diseases places a significant burden on the utilization of medical care, increases direct and indirect economic costs, and diminishes the quality of life [1].

ADs affect a significant proportion of the population, with more than 4% of the European population suffering from one or more of these diseases. Although all ADs share similarities in basic immunological mechanisms, in other aspects such as clinical manifestations and age of onset they vary widely [2,3].

Autoimmune thyroid disease (AITD) is a common organ-specific autoimmune disorder affecting mostly middle-aged women. AITD is a term that includes various clinical forms of autoimmune thyroiditis, such as Graves' disease, Hashimoto's (goitrous) thyroiditis, atrophic autoimmune hypothyroidism, postpartum thyroiditis, and thyroid-associated orbitopathy; two other rare types of AITDs include silent thyroiditis and iatrogenic thyroiditis [4]. Among these diseases, Hashimoto's thyroiditis and Graves' disease are the two most common types and share many features immunologically.

The hallmark of AITD is the production of antibodies to at least one of the main thyroid-specific autoantigens such as thyroglobulin (TG), thyroid peroxidase (TPO), thyroid stimulating hormone (TSH) receptor, and the relatively newly discovered sodium iodide transporter Ab [5].

Rheumatoid arthritis (RA) is a chronic inflammatory disease characterized by joint swelling, joint tenderness, and destruction of synovial joints, leading to severe disability and premature mortality [6,7].

Given the presence of autoantibodies, such as rheumatoid factor (RF) and anti-cyclic citrullinated peptide (anti-CCP), which can precede the clinical manifestation of RA by many years [8–11], RA is considered an AD [12,13]. Autoimmunity and the overall systemic and articular inflammatory load drive the destructive progression of the disease.

It was found that AITD can be associated with other ADs including type 1 diabetes [14,15], vitiligo [16], Addison's disease [17], and multiple sclerosis [18,19]. In contrast, RA as an AD can also cluster together with other ADs such as myasthenia graves, vitiligo, type 1 diabetes, and celiac disease [20].

An important question was raised concerning the clustering of autoimmune diseases together represented by autoimmune thyroid diseases and rheumatoid arthritis particularly with regards to seropositive and seronegative subtypes, and hence the aim of our study.

Aim

The aim of this work was to study the following:

(1) Thyroid dysfunction (hyperthyroidism or hypothyroidism) in seropositive versus seronegative RA patients;
(2) Autoimmune thyroid markers [anti-TPO, anti-TG, anti-TSH receptor antibodies (anti-TRAbs)] in seropositive versus seronegative RA patients;
(3) The relation between autoimmune thyroid markers [anti-TPO, thyroglobulin antibodies (anti-TG), and particularly TRAbs] and RA autoantibodies (anti-CCP and RF).

Patients and methods

Materials

The study was carried out on 70 consecutive patients with RA who were attending the rheumatology outpatient clinic or were inpatients in Alexandria Main University Hospital. They were divided according to the results of their serological tests (RF and anti-CCP) into two groups: group I, which included 35 patients with seropositive RA (positive to one or both seromarkers), and group II, which included 35 patients with seronegative RA (negative to both seromarkers). A third group (group III) that included 20 healthy age-matched individuals who were not suffering from any rheumatologic disorder was considered as the control group.

Inclusion criteria

Diagnosis of RA depended on the 2010 ACR-EULAR classification criteria [21]. A score of at least 6 out of 10 was needed for classification:

(1) Joint involvement was scored as follows: one large joint, 0; 2–10 large joints, 1; 1–3 small joints (with or without large joint affection), 2; 4–10 small joints (with or without large joint affection), 3; more than 10 joints (including at least one small joint), 5.
(2) Serology results were scored as follows (at least one test result is needed for classification): negative RF and negative anti-cyclic citrullinated peptide antibodies (ACPAs), 0; low-positive RF or low-positive ACPA, 2; high-positive RF or high-positive ACPA, 3.
(3) Acute-phase reactants (at least one test result is needed for classification) were scored as follows:

normal C-reactive protein (CRP) and normal erythrocyte sedimentation rate (ESR), 0; abnormal CRP or abnormal ESR, 1.
(4) Duration of symptoms was scored as follows: less than 6 weeks, 0; 6 or more weeks, 1.

Exclusion criteria

Patients receiving antithyroid drugs or corticosteroids or any immunosuppressive drugs known to alter the autoimmune markers or having a history of any thyroid disease or any other AD other than RA were excluded from the study.

Methods

All patients were subjected to the following:

Thorough history-taking

Thorough history of the patients were taken with emphasis on symptoms of thyroid dysfunction (hypofunction or hyperfunction of the thyroid gland) and symptoms of RA focusing on joint affection or any other systemic affection.

Complete physical examination

Complete physical examination was carried out with emphasis on any signs of thyroid dysfunction (hypothyroidism mostly presented by weight gain, easy fatigability, lethargy, cold intolerance, hair fall, depression, constipation, and others; hyperthyroidism mainly presented by tachycardia, excessive sweating, nervousness, hyperdefecation, heat intolerance, menstrual irregularities in females, weight loss, myopathy, and others [22]; joint examination for tenderness, swelling, deformity, and loss of function with disease activity score (DAS) for assessment of activity [23]. Joints on both right and left sides were assessed (five metacarpophalangeal joints, five proximal interphalangeal joints, knee, shoulder, elbow, and wrist). After assessment the results were interpreted as follows: less than 2.6, remission; 2.6–3.2, mild; 3.2–5.1, moderate; and more than 5.1, severe.

Laboratory investigations

Venous blood samples were drawn from every participant after an overnight fast of 8 h, and the patients were subjected to the following laboratory investigations:

(1) Routine: complete blood picture, ESR, CRP, renal function tests (serum urea and serum creatinine), and liver function tests (SGOT and SGPT).
(2) Rheumatologic assay using enzyme-linked immunosorbent assay (ELISA) to evaluate the RF [24,25] (normal, <15 IU/ml) and ACPA [26] (normal, <25 U/ml).
(3) Hormonal assay using ELISA technique:Serum thyroid stimulating hormone (TSH):(27-29) normal values: 0.4-4.6 mIU/L (30,31) (TSH< 0.4 mIU/L is considered hyperthyroidism and TSH> 4.6 mIU/L is considered hypothyroidism, Serum total T3: (32–35) normal values :0.8–1. 9 ng/mL, serum total T4 :normal values: 4. 7–12. 8 ug/dl [36,37].
(4) Thyroid autoantibodies using ELISA to evaluate serum anti-TPO antibodies [38] (normal, <50 IU/ml; borderline, 50–75 IU/ml; elevated, >75 IU/ml), serum anti-TG antibodies [39] (normal, <100 IU/ml; borderline, 100–150 IU/ml; elevated, >150 IU/ml), serum TRAbs [40,41] (negative, ≤1.1 U/l; equivocal, 1.1–1.5 U/l; positive, >1.5 U/l).

Neck ultrasound

A neck ultrasound was taken using a high-resolution linear transducer (7.5 MHz) Magic Agile Device (Kontron System, France) for assessment of the thyroid gland [42]. Proper patient positioning was critical to performing a high-quality ultrasound. The patient was made to lie flat, and adequate neck extension was achieved by placing pillows under the shoulders. A coupling gel was then placed on the transducer to enhance image generation. The transducer was then moved over the patient's neck to obtain a series of images of the thyroid gland and other neck structures. Reports included measurement of thyroid gland size, architecture, blood flow on Doppler evaluation, presence of nodules, nodule size and characteristics, and any other periglandular pathology such as neck lymph nodes or parathyroid glands. In addition, evidence of compression or displacement of adjacent structures like the trachea or internal jugular vein was assessed [43,44].

The size of the thyroid was calculated in milliliters as the sum of the volumes of both lobes (isthmus is neglected). The volume of one thyroid lobe was calculated as follows: V (ml) = width × depth × length × 0.479 (cm). The normal thyroid volume in females is lower than 18 ml and that in males is lower than 22 ml. The typical thyroid ultrasonography (TUS) appearance of autoimmune (Hashimoto's) thyroiditis includes focal or diffuse glandular enlargement with coarse, heterogeneous, and hypoechoic parenchymal echo-pattern. Presence of multiple discrete hypoechoic micronodules (1–6 mm size) is strongly suggestive of chronic thyroiditis. Fine echogenic fibrous septae may produce a pseudolobulated appearance of the parenchyma. Color Doppler may demonstrate slight to markedly increased vascularity of the thyroid parenchyma similar to thyroid inferno sign [45–47].

Statistical analysis [48]

Data were fed into a computer and analyzed using IBM SPSS software (version 20.0; SPSS Inc., Chicago, Illinois, USA) [49]. Comparison between different groups regarding categorical variables was made using the χ^2-test. When more than 20% of cells had an expected count less than 5, correction for χ^2 was conducted using Fisher's exact test or Monte Carlo correction. The distribution of quantitative variables was tested for normality using the Kolmogorov–Smirnov test, the Shapiro–Wilk test, and the D'Agstino test. Histograms and QQ plots were used for vision test. If the data were normally distributed, parametric tests were applied. If the data were abnormally distributed, nonparametric tests were used. For normally distributed data, comparison between more than two populations was made using the *F*-test (ANOVA) and the post-hoc test (Scheffe). For abnormally distributed data, the Kruskal–Wallis test was used to compare between different groups and pairwise comparison was made using the Mann–Whitney test. Significance test results are quoted as two-tailed probabilities. Significance was judged at the 5% level.

Informed consent was taken from each participant, and local ethical committee approval was obtained.

Results

Clinical and laboratory characteristics of rheumatoid arthritis patients (group I and group II) as compared with controls

The three studied groups were age matched (Table 1).

RA duration was significantly higher in group I versus group II (Table 1).

ESR was significantly higher in group I than in group III, and higher in group II than in group III; CRP was higher in group I than in group III and higher in group II than in group III (Table 1).

RF was significantly higher in group I than in group II and group III, and higher in group II than in group III; anti-CCP was higher in group I compared with group II and group III (Table 1).

No significant statistical difference was observed among the studied groups as regards serum TSH, T3, and T4 (Table 1).

Significant statistical difference was observed between the studied groups as regards anti-TPO: it was higher in group I than in groups II and III, and higher in group II than in group III (Table 1).

Significant statistical difference was observed between the studied groups as regards anti-TG: it was higher in group I than in groups II and III, and higher in group II than in group III (Table 1).

Significant statistical difference was observed among the studied groups as regards TRAb levels: it was higher in group I compared with group II, and higher in group I compared with group III (Table 1).

It was observed that 88.6% of group I were female and 11.4% were male, whereas 94.3% of group II were female and 5.7% were male; in group III 80% were female and 20% were male (Fig. 1).

According to the DAS28, 62.9% of group I had severe disease, 31.4% had moderate disease, and 5.7% had mild

Table 1 Clinical and laboratory characteristics of rheumatoid arthritis patients (group I and group II) compared with control (group III)

Characteristic of comparison	Group I	Group II	Group III	*P* value
Age	46. 23 ± 11.90	44.97 ± 13.01	46.20 ± 15.88	0.910
Sex		Fig. 1		
RA duration	5.73 ± 6.78	2.62 ± 3.13	—	0.018*
DAS28 score		Fig. 2		
Clinical picture of thyroid dysfunction (hypo/eu/hyper)		Fig. 3		
ESR	46.11 ± 30.79	45.11 ± 30.21	21.15 ± 9.67	0.002*
CRP (mg/l)	23.86 ± 26.31	26.46 ± 41.60	5.19 ± 2.08	<0.001*
RF (IU/ml)	112.49 ± 181.77	8.29 ± 3.49	6.24 ± 3.30	<0.001*
Anti-CCP (U/ml)	128.47 ± 149.74	9.27 ± 6.08	7.12 ± 4.99	<0.001*
TSH (mIU/l)	3.38 ± 5.12	2.55 ± 3.43	1.89 ± 1.11	0.883
T3 (ng/ml)	1.46 ± 0.44	1.31 ± 0.47	1.41 ± 0.30	0.312
T4 (μg/dl)	9.32 ± 2.95	8.22 ± 1.89	8.30 ± 1.64	0.107
Anti-TPO (IU/ml)	1301.9 ± 1716.0	799.4 ± 1597.7	30.26 ± 12.96	<0.001*
Anti-TG (IU/ml)	1750.0 ± 1866.2	898.1 ± 988.11	61.94 ± 87.31	<0.001*
TRAbs (U/l)	1.03 ± 1.03	0.69 ± 0.37	0.56 ± 0.38	0.006*

CCP, cyclic citrullinated peptide; CRP, C-reactive protein; DAS, disease activity score; ESR, erythrocyte sedimentation rate; RA, rheumatoid arthritis, RF, rheumatoid factor; TG, thyroglobulin; TPO, thyroid peroxidase; TRAb, TSH receptor antibody; TSH, thyroid stimulating hormone; *Significant.

disease. In group II, 45.7% had severe disease, 45.7% had moderate disease, and 8.6% had mild disease (Fig. 2).

As regards the clinical picture of thyroid dysfunction in the three studied groups, in group I 62.9% of patients were clinically euthyroid, 22.9% were clinically hypothyroid, and 14.3% were clinically hyperthyroid; in group II 65.7% of patients were clinically euthyroid, 25.7% of patients were clinically hypothyroid, and 8.6% of patients were clinically hyperthyroid (Fig. 3).

It was found that hypothyroidism was more common than hyperthyroidism. In group I, 86.6% had normal TSH, 28.6% were hypothyroid, and 2.9% were hyperthyroid; as regards T3, 85.7% had normal T3 and 14.3% had abnormal T3; and as regards T4, 85.7% had normal T4 and only 14.3% had abnormal T4. In group II, as regards TSH, 62.9% had normal TSH, 28.6% were hypothyroid, and 8.6% were hyperthyroid; as regards T3, 91.4% had normal T3, whereas 8.6% had abnormal T3; and as regards T4, 94.3% had normal T4 and only 5.7% had abnormal T4. In group III, as regards TSH, 85% had normal TSH and 15% were hypothyroid, whereas as regards T3 and T4 100% had normal levels (Table 2).

It was found that, in group I, 100% were positive for anti-TPO and anti-TG, whereas as regards TRAbs 91.4% were negative, 5.7% were positive, and 2.9% were equivocal. In group II, 100% were positive for anti-TPO; as regards anti-TG, 82.9% were positive, 8.6% were equivocal, and 8.6% were negative; and as regards TRAbs 80% were negative, 14.3% were equivocal, and 5.7% were negative. In group III, 95% were negative for anti-TPO and 5% were equivocal; as regards anti-TG, 85% were negative, 10% were equivocal, and 5% were positive; and as regards TRAbs, 95% were negative and 5% were equivocal (Table 3).

Table 2 The percentage of thyroid stimulating hormone, T3 and T4 among the studied groups

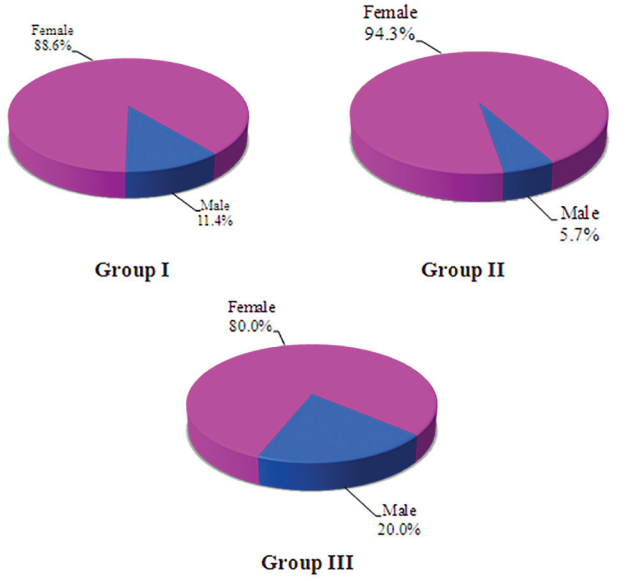
Thyroid function tests	*N* (%)		
	Group I (*n* = 35)	Group II (*n* = 35)	Group III (*n* = 20)
TSH			
Hyperthyroid (<0. 4)	1 (2.9)	3 (8.6)	0
Normal (0.4–4.6)	24 (68.6)	22 (62.9)	17 (85)
Hypothyroid (>4.6)	10 (28.6)	10 (28.6)	3 (15)
T3 (ng/ml)			
Normal (0.8–1.9)	30 (85.7)	32 (91.4)	20 (100)
Abnormal	5 (14.3)	3 (8.6)	0
T4 (μg/dl)			
Normal (4.7–12.8)	30 (85.7)	33 (94.3)	20 (100)
Abnormal	5 (14.3)	2 (5.7)	0

TSH, thyroid stimulating hormone.

Ultrasound evidence of thyroiditis in rheumatoid arthritis patients (group I and group II) compared with control (group III)

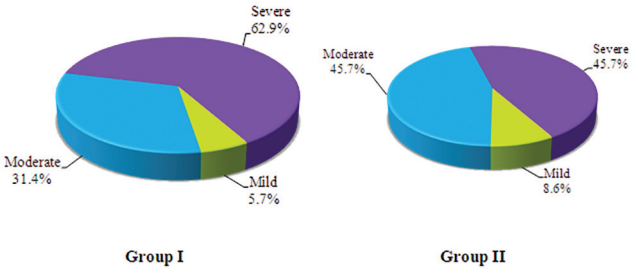
Evidence of thyroiditis was found in 34.3% of group I and 51.4% of group II versus no ultrasound evidence of thyroiditis in the control group. A statistically significant difference was observed between the studied groups as regards ultrasound evidence of thyroiditis (between

Figure 1



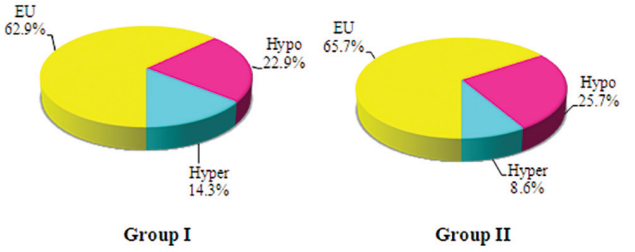
A figure comparing the sex of the different studied groups.

Figure 2



Comparison between the studied groups according to DAS 28 score.

Figure 3



Comparison of the clinical picture of thyroid disorders between the studied groups.

group I and group III and between group II and group III), whereas there was no statistically significant difference between group I and group II (Table 4).

Correlation between rheumatoid factor and thyroid autoantibodies

There was a statistically significant positive correlation between RF and anti-TPO among all patients (seropositive and seronegative) with RA (r = 0.318, P = 0.007), as well as between RF and TRAbs (r = 0.300, P = 0.021), whereas there was no statistically significant correlation between RF and anti-TG (r = 0.234, P = 0.052) (Table 5 and Figs. 4 and 5).

Correlation between anti-cyclic citrullinated peptide and thyroid autoantibodies

There was a statistically significant positive correlation between anti-CCP and anti-TPO among all patients(seropositive and seronegative) with RA (r = 0.336, P = 0.004), as well as between anti-CCP and TRAbs (r = 0.252, P = 0.035), whereas there was no statistically significant correlation between anti-CCP and anti-TG (r = 0.204, P = 0.90) (Table 6 and Figs. 6 and 7).

Discussion

AITD is a term used to bring together a group of pathologies that involve thyroid dysfunction and an autoimmune response against this endocrine organ as its hallmark [50,51]. RA is an AD with chronic inflammation characterized by joint swelling, joint tenderness, and destruction of synovial joints, leading to severe disability and premature mortality [6,7,12,13]. The relationship between RA and the thyroid gland has been studied extensively, with several studies demonstrating the autoimmune nature of thyroid dysfunctions in RA; however, the exact pathogenic mechanism is still unclear [52,53].

We designed this work to study the presence of thyroid dysfunction (hyperthyroidism or hypothyroidism)

Table 3 The percentage of anti-thyroid peroxidase, antithyroglobulin, and thyroid stimulating hormone receptor antibodies among the studied groups

Thyroid autoantibodies	Group I (n = 35) (%)	Group II (n = 35) (%)	Group III (n = 20) (%)
Anti-TPO (IU/ml)			
Negative (<50)	0	0	95
Equivocal (50–75)	0	0	5
Positive (>75)	100	100	0
Anti-TG (IU/ml)			
Negative (<100)	0	8.6	85
Equivocal (100–150)	0	8.6	10
Positive (>150)	100	82.9	5
TRAbs			
Negative (<1.1)	91.4	80	95
Equivocal (1.1–1.5)	2.9	14.3	5
Positive (>1.5)	5.7	5.7	0

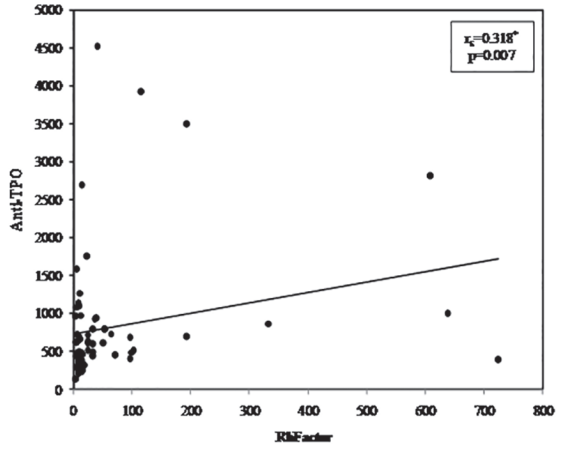
TG, thyroglobulin; TPO, thyroid peroxidase; TRAb, TSH receptor antibody.

Table 4 Ultrasound evidence of thyroiditis among the studied groups

Thyroid ultrasonography	Group I (n = 35)	Group II (n = 35)	Group III (n = 20)	χ^2	P
Thyroiditis [n (%)]					
No	23 (65.7)	17 (48.6)	20 (100)	15.171**	0.001**
Yes	12 (34.3)	18 (51.4)	0 (0.0)		
Significance between groups		I–III**, II–III***			

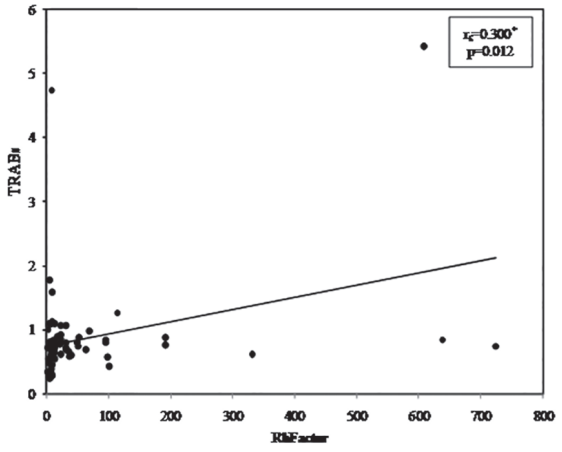
*Statistically significant at $p \leq 0.05$; **Statistically significant at $p \leq 0.01$; ***Statistically significant at $p \leq 0.001$

Figure 4



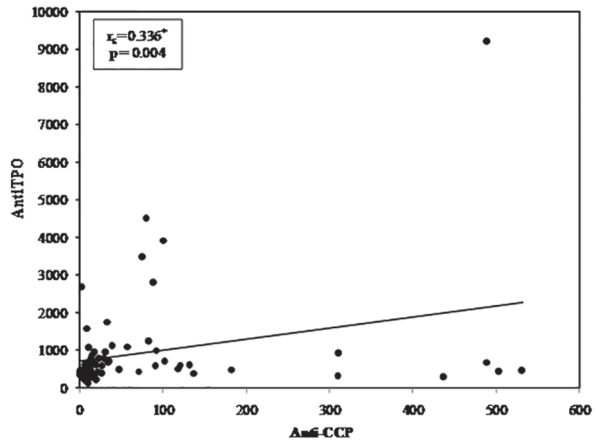
The correlation between rheumatoid factor (RF) and anti-thyroid peroxidase (anti-TPO).

Figure 5



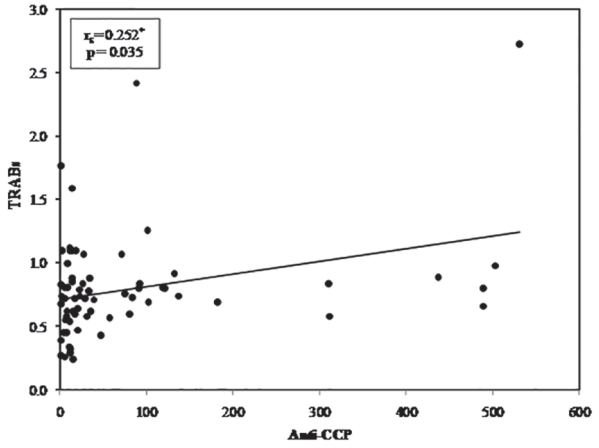
The correlation between rheumatoid factor (RF) and TSH receptor antibodies (TRAbs).

Figure 6



The correlation between anti-cyclic citrullinated peptide (anti-CCP) and anti-thyroid peroxidase (anti-TPO).

Figure 7



The correlation between anti-cyclic citrullinated peptide (anti-CCP) and TSH receptor antibodies (TRAbs).

Table 5 Correlation between mean rheumatoid factor and anti-thyroid peroxidase, antithyroglobulin, and thyroid stimulating hormone receptor antibodies autoantibodies

Thyroid autoantibodies	RF (total patients)
Anti-TPO	
r_s	0.318
P	0.007*
Anti-TG	
r_s	0.234
P	0.052
TRAbs	
r_s	0.300
P	0.012*

r_s, Spearman's coefficient; TG, thyroglobulin; TPO, thyroid peroxidase; TRAb, TSH receptor antibody; *Significant.

Table 6 Correlation of anti-cyclic citrullinated peptide with anti-thyroid peroxidase, antithyroglobulin, and thyroid stimulating hormone receptor antibodies autoantibodies

Thyroid autoantibodies	Anti-CCP (total patients)
Anti-TPO	
r_s	0.336
P	0.004*
Anti-TG	
r_s	0.204
P	0.90
TRAbs	
r_s	0.252
P	0.035*

CCP, cyclic citrullinated peptide; r_s, Spearman's coefficient; TG, thyroglobulin; TPO, thyroid peroxidase; TRAb, TSH receptor antibody; *Significant.

in seropositive versus seronegative RA patients, as well as to study the presence of autoimmune thyroid markers such as anti-TPO, anti-TG, and particularly TRAbs in seropositive versus seronegative RA patients.

Our study showed no significant difference between patients with RA and controls in relation to age in agreement with the designed protocol of our study.

It was found that about 89% of our patients in group I (seropositive RA) were female versus 11% who were male, whereas in group II (seronegative RA) around 94% were female versus 6% who were male. Our results were consistent with other studies that showed female predominance in the course of RA, such as those performed by Kvien *et al.* [54] and Del Rincón *et al.* [55].

DAS28 as an indicator of disease activity in RA was assessed in our study and it was found that around 63% of group I (seropositive) had severe disease activity versus around 46% in group II (seronegative); 31% had moderate activity in group I versus 46% in group II; and 6% had mild activity in group I versus 9% in group II.

Clinical features of thyroid dysfunction, either hypothyroidism or hyperthyroidism, were thoroughly assessed in our study. Sixty-three percent of patients in group I (seropositive) versus 66% in group II (seronegative) were clinically euthyroid; 23% in group I versus 26% in group II had suggestive symptoms of hypothyroidism; and features of hyperthyroidism were consistent in 14% of patients in group I versus 9% of patients in group II.

RF has been widely used as a screening test for patients with arthritis. Moreover, it constitutes one of the classification criteria proposed by the ACR [56,57]. Relative to RF, more recently, anti-CCP has been attributed to RA. About 35–40% of RF-negative patients are ACPA positive [58]. ACPAs are now well

suited as a frontline diagnostic test for RA, especially early RA. It should be mentioned that patients can be classified according to their RF and ACPAs assay into seropositive (positive to one or both of them) and seronegative (negative to both), and hence ACPAs in RF-negative patients can be helpful in confirming the diagnosis of RA. Moreover, a recent study by Binesh *et al.* [59] compared the diagnostic value of anti-CCP and RF in patients with RA and revealed that combination of anti-CCP and RF tests rather anti-CCP or RF alone gives the best results in the diagnosis of RA.

A significant statistical difference was observed among the studied groups regarding RF: it was higher in group I than in groups II and III, and higher in group II than in group III. As regards anti-CCP, significant statistical difference was observed between the studied groups: it was higher in group I compared with groups II and III.

Our study demonstrated a higher incidence of thyroid dysfunction (mainly hypothyroidism) in patients with RA, whether seropositive or seronegative, compared with controls. This is consistent with many studies, such as the one by El-Sherif *et al.* [60] in which was reported a higher incidence of thyroid dysfunction in patients with RA and also in their families versus normal individuals.

Another study by Shiroky *et al.* [53] conducted on 91 RA patients evaluated thyroid dysfunction and found that 30% of patients had evidence of thyroid disorders compared with 11% of controls. They concluded that thyroid dysfunction — namely, hypothyroidism — is three-fold higher in patients with RA versus controls [53]. However, a study conducted by Silman *et al.* [61] on 80 patients (41 male and 39 female; mean age 11.5 ± 4.1 years) demonstrated no significant difference in the incidence of AITDs in RA patients as compared with controls. They concluded that there was no need to screen routinely for the presence of thyroid dysfunction in patients with RA. This finding is most probably attributed to the fact that the study was conducted on young patients [61].

In our study hypothyroidism was more prevalent than hyperthyroidism in patients with RA (both group I and group II): 29% of patients in both groups were hypothyroid, whereas 3% in group I and 9% in group II were hyperthyroid.

A strong evidence of higher incidence of hypothyroidism as compared to hyperthyroidism in patients with RA was found in many reviews and studies where in China 2003, Porkodi R *et al.* studied the prevalence of thyroid dysfunction on 800 patient with RA. The referred study showed 73% incidence of hypothyroidism versus 5% of his studied patients were hyperthyroid, this high incidence is mostly attributed to patient selection where those with known thyromegaly or evidence of thyroid dysfunction were included in the study [62].

It was found that there was no statistically significant difference among the studied groups as regards mean serum TSH, T3, and T4 levels. However, Singh *et al.* [63] found a statistically significantly higher mean serum T4 level in patients with RA as compared with controls and correlated this increased incidence to the duration of illness of RA.

Moreover, in the study conducted by Wellby *et al.* [64], mean serum TSH was within normal range in all of the studied RA patients, whereas there was significant decrease in serum T3 and T4 in patients compared with controls. This finding was probably because they studied the incidence of thyroid dysfunction in patients with recent-onset RA [64].

It was shown in our study that, in patients with RA (group I and group II), there were higher mean levels of autoimmune thyroid markers — namely, anti-TPO and anti-TG antibodies — as compared with controls, suggesting increased incidence of AITDs. Moreover, in our study there was a statistically significant difference in the mean level of anti-TPO and anti-TG antibodies according to the serostatus of RA patients (higher levels in seropositive vs. seronegative patients).

Our results are consistent with those of Raterman *et al.* [65] who concluded from the CARRE' study conducted on 353 patients with RA that higher levels of TPO antibodies were present in patients with RA when compared with controls.

In our study it was found that in group I 100% were positive for anti-TPO and anti-TG, whereas in group II 100% were positive for anti-TPO, 82.9% were positive for anti-TG, 8.6% were equivocal, and 8.6% were negative. In group III, 95% were negative for anti-TPO and 5% were equivocal; as regards anti-TG, 85% were negative, 10% were equivocal, and 5% were positive. Similar results were found by Porkodi *et al.* [62]: anti-TPO antibodies were positive in 88% and anti-TG in 56% of RA patients.

Innocencio *et al.* [66] have reported positivity for anti-TG and anti-TPO of 32 and 4%, respectively. This was also emphasized by Başkan *et al.* [67], who found positive anti-TPO and anti-TG in 2.6 and 5.1%, respectively, among 92 RA patients in Turkey.

In 2013, Koszarny *et al.* [68] measured the level of antithyrotropin receptor antibodies (TRAbs), and found that TRAbs were not detected in any of the RA patients. We detected the level of TRAbs in a small proportion of our RA patients (four patients were positive and six were equivocal): in group I (seropositive RA) the majority were negative for TRAbs (91.4%), 2.9% were equivocal, and 5.7% were positive, whereas in group II (seronegative RA) 80% were negative, 14.3% were equivocal, and 5.7% were positive for TRAbs.

Andonopoulos *et al.* [69] studied thyroid functions and immune profile in patients with RA. They measured thyroid functions, antibodies to TPO (anti-TPO), and TRAbs. He found a high level of anti-TPO in patients with RA, whereas no one had high TRAb levels. Moreover, he concluded that there was no detectable association between thyroid abnormalities and any serological RA findings in his study [69].

In contrast to our study, Koga *et al.* [70] studied thyroid autoimmune disorders in patients with juvenile idiopathic arthritis. They measured the levels of anti-TPO, anti-TG, and thyroid receptor antibodies, both blocking and stimulatory ones, and concluded that high levels of both TSH receptor stimulatory and blocking antibodies were present in patients with RA with higher incidence of positivity to TSH receptor stimulatory than the blocking ones [70].

Our study revealed a higher mean level of anti-TPO, anti-TG, and TRAbs in patients with RA regardless of their serostatus when compared with controls. Moreover, higher levels of anti-TPO, anti-TG, and TRAbs were detected in patients with seropositive RA (group I) versus seronegative RA (group II), suggesting a higher incidence of autoimmune process in seropositive versus seronegative patients.

In a trial to link the two ADs together, we observed a significant positive correlation between anti-TPO, TRAbs, and RF titer, but failed to observe any statistically significant positive correlation between anti-TG levels and RF.

In agreement with our results, Raterman *et al.* [71] concluded from his study conducted on 353 patient with RA that a higher percentage of anti-TPO-positive patients were among those with high RF titer with a significant positive correlation between the two autoantibodies.

In contrast, in the study by Yavasoglu *et al.* [72], it was suggested that antithyroid autoantibodies are independent of the RF titer.

Moreover, the prognostic autoantibody in RA — namely, anti-CCP — was also found to be significantly correlated with anti-TPO and TRAb levels in patients with RA. This finding goes with the previously discussed common autoimmune process involving both diseases; however, no statistically significant correlation was found between anti-TG and ACPAs. In 2011 Charles and colleagues did not find a relationship between the presence of thyroid autoantibodies and anti-CCP positivity [65,73].

Evidence of thyroiditis by thyroid ultrasonography in our study was seen in 34% of patients in group I (seropositive) versus 51% in group II (seronegative), whereas none of the individuals in the control group showed any suggestive signs of thyroiditis on ultrasonography. No statistically significant difference was found in our study with respect to ultrasound findings between seropositive versus seronegative groups; however, a significant difference was observed between patients and controls.

In a study conducted by Przygodzka and Filipowicz-Sosnowska [74], suggestive signs of thyroiditis in thyroid ultrasonography in RA patients were in the form of heterogenicity of thyroid tissue in 5% of patients and diffuse hypoechogenicity in 2%.

In 2010, Lee *et al.* [75] screened 110 RA patients for thyroid disorders by thyroid ultrasonography and came across an interesting finding: he detected a high incidence of papillary thyroid cancer in patients with RA and most of the thyroid cancer patients had a solid and hypoechoic pattern in thyroid ultrasonography.

Conclusion

Thyroid dysfunction and AITD are common in RA patients, with hypothyroidism being the most common disorder. Hypothyroidism is prevalent in 29% of patients regardless of their serostatus. This association is independent of disease activity assessed by DAS28. Increased incidence of thyroid autoimmunity was seen in seropositive RA versus seronegative RA patients, as evidenced by higher levels of thyroid autoimmune markers in the former. TRAbs were detectable in a small subset of patients with RA.

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Conflicts of interest

There are no conflicts of interest.

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