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*Full Length Research Paper*

# Presence of Thyroid Disorders in Patients with Autoimmune and Autoinflammatory Rheumatic Diseases

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**Association between rheumatological and thyroid disorders has been demonstrated by many studies. Our aim was to evaluate the prevalence of thyroid disorders in patients with autoimmune (ARD) and also autoinflammatory rheumatic disease (AIRD). We evaluated serum levels of thyroid-stimulating hormone (TSH), free triiodothyronine (fT3), and free thyroxine (fT4), and titers of antithyroglobulin (TG-Ab) and antithyroid peroxidase (TPO-Ab) antibodies in 298 patients with ARD and 363 patients with AIRD. We also recruited 137 age-matched controls. Ultrasonography (US) of the thyroid gland was performed in all subjects. Comparisons were done only among participants of the same gender. Hashimoto's thyroiditis (HT) frequency was significantly more frequent in patients with ARD or AIRD in female population and also it was more frequent in patients with ARD in male population than in controls. In both female and male patients with ARD, mean TPO-Ab levels was lower than those receiving biologics than those receiving disease-modifying antirheumatic drugs (DMARDs), but difference was not significant. Receiving nonsteroidal anti-inflammatory drug (NSAID) was more frequent in female patients with ARD and AIRD and also in controls than those not having HT. Our study shows a significantly higher prevalence of thyroid autoimmunity in patients with ARD and AIRD as compared to controls. Female gender has an important role for HT diagnosis. We suggest that thyroid function tests should be a part of the clinical evaluation particularly in female patients and also male patients with ARD and AIRD.**

**Keywords:** Autoimmunity, Autoinflammation, Biologic agent, Hashimoto's Thyroiditis, Rheumatic Disease.

## INTRODUCTION

Immune system has two main parts; innate and adaptive immunity. Innate immunity represents the first barrier in host immune defense; it identifies pathogens or other harmful triggers inducing an inflammatory process to block their diffusion and activates adaptive immunity. The effector cells of innate immunity are phagocytes, including macrophages, dendritic cells, and other antigens presenting cells (APC) (Theofilopoulos et al., 2010). Adaptive immunity involves B cells, T cells, cytotoxic T cells, and antibody production also is characterized by highly specific antigen recognition through specific antigen receptors: B and T cell receptors (BCR and TCR) (Doria et al., 2012).

Recently, researchers have been described that the diseases which have abnormal innate immune responses without the involvement of autoantibodies or autoreactive T cells are identified as autoinflammatory, however diseases that depend on autoreactive B or T cells are termed as autoimmune (McGonagle and

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McDermott, 2006). Autoimmune diseases (AD) have been classified according to the target of the abnormal immune response: organ spesific and non-organ spesific. For instance, HT is an organ-specific autoimmune disease involving a specific immune attack on thyroid gland, whereas rheumatoid arthtritis (RA) is systemic AD, in which multiple organs are targeted and also autoimmune responses to multiple antigens can be measured (Galeazzi et al., 2006).

Autoinflammatory diseases (AID) have been firmly linked to mutations in inflammasome forming NOD-like reseptors (NLRs). Indeed, the majority of patients with AIDs have mutations in pyrin, cryopirin, and tumor necrosis factor (TNF) receptor super-family genes (Aksentijevich et al., 2007).

HT is characterized by lymphocytic infiltration and destruction of the thyroid gland and presence of thyroid autoantibodies including serum TPO-Ab and TG-Ab (Dayan and Daniels, 1996). The HT's relationship with ARDs such as systemic lupus erythematosus (SLE), Sjögren's syndrome (SjS), systemic sclerosis (SSc), or RA has been observed by many studies (Chan et al., 2001; Scofield, 1995). Furthermore etiological possibilities are also being discussed for AIRDs such as spondyloarthopaties (SpA) include psoriatic arthritis (PsA), undifferentiated spondyloarthritides (UspA), reactive arthritis (ReA), enteropathic spondyloarthritidis (EA) (Peluso et al., 2011) and ankylosing spondylitis (AS) (Lange et al., 1999).

In the present study, we investigated the frequency of HT and thyroid disorders in our patients with ARD and AIRD compared to controls.

## PATIENTS AND METHODS

Participants were recruited from the rheumatology out-patients' clinics of Sakarya University Hospital. Clinical records and laboratory data of the patients fulfilling the diagnostic criteria for patients with ARD such as seropositive RA, seronegative RA, SLE, primary Sjogren's syndrome (PSS), SSc, polymyositis (PM), dermatomyositis (DM), mixed connective tissue disease (MCTD), and also for patients with AIRD such as familial mediterranean fever (FMF), Behcet's disease, gout, AS, ReA, EA, PsA, adult-onset still disease (AOSD) were reviewed. In addition the data of age and sex matched controls were reviewed. We conducted a retrospective cohort study which was approved by the Hospital's Ethics Committee.

The presence of thyroid dysfunction was estimated by clinical evaluation and using serum determination of fT3, fT4, TSH, TPO-Ab, and TG-Ab using immunochemiluminescence (Cobas, Roche Diagnostics, Indianapolis, IN, USA). Normal ranges for fT3 and fT4 were 2.62-5.69 pmol/L and 9-19.04 pmol/L, respectively. Subclinical hypothyroidism was defined as an elevation of TSH above the upper limit of the reference range (0.34-4.94 μIU/mL) with normal fT3 and fT4 concentrations; subclinical hyperthyroidism was defined as a decreased serum TSH with normal fT3 and fT4. Patients with hyperthyroidism were characterized by low TSH levels and elevated values of fT4, fT3 or both. Patients were considered to have hypothyroidism when they demonstrated elevated TSH concentrations and low fT4. Values for TPO-Ab and TG-Ab above 5.61 and 4.11 respectively were considered positive. Diagnosis of HT was made in the presence of elevated TPO-Ab and/or TG-Ab values and of a typical pattern of the thyroid US (Weetman, 2004).

Thyroid US was performed with Logic C3 (GE medical system, Milwaukee, USA) equipped with a linear transducer operating at 8.5–13 mHz. A physician who is blinded to laboratory findings performed thyroid sonography in all subjects in order to define following parameters; thyroid parenchyma echogenicity, presence of nodule formation, echo structure of nodules (solid, cystic, or mixed), echogenicity (hyper, iso, or hypoechoic) of thyroid gland, margins of the nodules (well-defined, irregular, blurred), and presence of calcifications in the nodules.

Statistical analysis was performed using SPSS statistical software, version 20.0. Quantitative variables (clinical, laboratory, US parameters) were given as the mean and SD. Because of the different female:male ratios among groups and female gender is a well-recognized risk factor for HT and thyroid disorders, levels of TSH, fT3, fT4, TPO-Ab and TG-Ab, thyroid US findings, TPO-Ab and TG-Ab positivity were compared only among participants of the same gender. In same gender; subjects were devided into three groups : Patients with ARD, Patients with AIRD, and controls. Levene's statistic was used for homogeneity of variances. Mean group values were compared using one-way analysis of variance (ANOVA) for normally distributed variables. The chi-squared test was used to compare cases and controls. Odds ratio (OR) and corresponding 95% confidence intervals (CI) were calculated based on observed values. Any *P* value less than 0.05 was considered statistically significant.

## RESULTS

*General Results:* The mean ages of patients in ARD, AIRD, and control groups were 47.4 ± 11.8, 42.6 ± 10.7, and 46.4 ± 9.4 years, respectively. The diseases and demographic features of the 298 patients with ARD were as follows: 79 patients with seropositive RA (63 women, 16 men; mean age: 49.7 ± 11.2 years), 76 patients with seronegative RA (50 women, 26 men; mean age: 47.3 ± 13.1 years), 54 patients with SLE (51 women, 3 men; mean age: 41.5 ± 11.3 years), 52 patients with PSS (50 women, 2 men; mean age: 50.1 ± 10 years), 23 patients with SSc (23 women; mean age: 47 ± 11.9 years), 6 patients with PM (4 women, 2 men; mean age: 44.6 ±

10.9 years), 2 patients with DM (1 woman, 1 man; mean age: 47.5 ± 6.3 years), 6 patients with MCTD (5 women, 1 man; mean age: 54.8 ± 8.3 years), also diseases and demographic features of 363 patients with AIRD were as follows: 33 patients with FMF (26 women, 7 men; mean age: 35.1 ± 12.3 years), 64 patients with Behcet's disease (41 women, 23 men; mean age: 40.4 ± 9.3 years), 26 patients with gout (14 women, 12 men; mean age: 50.5 ± 7.5 years), 111 patients with AS (14 women, 12 men; mean age: 40.3 ± 9.3 years), 16 patients with ReA (6 women, 10 men; mean age: 42.8 ± 10.6 years), 6 patients with EA (3 women, 3 men; mean age: 47.8 ± 9.1 years), 96 patients with PsA (69 women, 27 men; mean age: 46.3 ± 10.9 years), 11 patients with AOSD (4 women, 7 men; mean age: 46.4 ± 10.7 years).

There were no statistically significant differences about age, sex, BMI and disease duration among groups (data is shown in Table 1). The frequencies of TPO-Ab positivity, HT, and thyroid dysfunction in patients are given in Table 2.

*Results in Females:* Mean BMI, TSH, TPO-Ab, TG-Ab levels were higher and also TPO-Ab positivity, hypoechoic pattern, and HT frequency were more frequent in female than in male population among groups, as predicted (p=0.00, p=0.00, p=0.00, p=0.00 and p=0.001, p=0.002, p=0.01 respectively).

Thyroid dysfunction was found in 34 of 247 women (13.7%): subclinical hypothyroidism in 17 (6.9%), hypothyroidism in 4 (1.6%),subclinical hyperthyroidism in 10 (4%) and hyperthyroidism in 3 (1.2%) patients with ARD. In addition thyroid dysfunction was found in 26 of 210 women (13.4%): subclinical hypothyroidism in 18 (8.6%), hypothyroidism in 3 (1.4%), and subclinical hyperthyroidism in 5 (2.4%) patients with AIRD. All the subjects of control group were euthyorid. Thyroid dysfunction frequency was nonsignificant between ARD and AIRD (*P*=0,56). Among patients with subclinical hypothyroidism 2 (2.3%) patients with ARD and 7(13%) patients with AIRD, patients with hypothyroidism 4 (4.5%) patients with ARD and 1(1.9%) patients with AIRD also among patients with subclinical hyperthyroidism 4(4.5%) patients with ARD and 4(2.6%) patients with AIRD met the criteria for HT. All patients with hypothyroidism was also diagnosed HT in ARD group (*P*=0.018). In AIRD group more than half of the patients with subclinical hyper-hypothyroidism were diagnosed HT. No correlation between disease duration, BMI or age and thyroid dysfunction were detected in patients with ARD or AIRD (ARD; *P:* 0.55, *P*:0.426, *P*:0.082 and AIRD; *P:* 0.917, *P*:0.91, *P*:0.889, respectively).

Serum fT4 values were significantly higher in patients with ARD or AIRD (*P*=0.035, *P*=0,025) as compared to controls, as were TG-Ab (*P*=0.00, *P*=0.00) and TPO-Ab levels (*P*=0.00, *P*=0.00). TPO-Ab and TG-Ab positivity was evaluated in 77 (31.2%) and 85 (34.4%) patients with ARD and in 49 (23.3%) and 56 (26.7%) patients with AIRD, also 2 (1.9%) and 2 (1.9%) subjects in controls. The patients with ARD and AIRD have more frequent TPO-Ab positivity than controls (*P*=0.00, *P*=0.00), also the patients with ARD have more frequently TPO-Ab positivity than the patients with AIRD, whereas the difference was not significant (*P*=0.06). In patients with ARD mean TPO-Ab and TG-Ab values were higher than AIRD but not significant (*P*=0.062, *P*=0.074). Although there was no difference in frequency of hypothyroidism between TPO-Ab positive and negative patients with AIRD (*P*= 0.23), TPO-Ab positive patients with ARD had more hypotroidism frequency than TPO-Ab negative patients (*P*= 0.01). The risk of developing hypothyroidism was greater in TPO-Ab-positive patients with ARD (OR = 8.6, 95% CI 3–21.3, *P*= 0.001).

HT was significantly more frequent in patients with ARD and AIRD than in controls (P=0.00, P=0.00). In addition the patients with ARD had HT more frequently than the patients with AIRD (P=0.022). Compared to the patients with AIRD and controls, the OR for patients with ARD for having HT was 27.9 (95% CI 6.7-116, *P*= 0.000). Moreover the OR for patients with AIRD for having HT was 17.4 (95% CI 4.1-73.2, *P*= 0.000). There was no significant difference in age or BMI between the patients with having and not having HT among groups (ARD: *P*=0.98, *P*=0.42 and AIRD: *P*=0.78, *P*=0.13 and controls: *P*=0.18, *P*=0.65).

There was no significant difference between patients with a disease duration ≤ 2 years and patients with a disease duration > 2 years in prevalence of HT in both ARD and AIRD groups (*P*=0.21, *P*=0.14). TPO-Ab positivity was more frequent in patients with a disease duration ≤ 2 years than in patients with a disease duration > 2 years in ARD group (*P*=0.048). In multivariable analysis, the ORs for patients with ARD and AIRD those disease duration ≤ 2 years compared to the patients with disease duration > 2 years were 1.4 (95% CI 0.8-2.4, *P*= 0.21) and 1.6 (95% CI 0.8-3.1, *P*= 0.15) for HT frequency, respectively. Furthermore the ORs for patients with a disease duration ≤ 2 years compared to the patients with a disease duration > 2 years in ARD and AIRD groups 1.7 (95% CI 1-3.1, *P*= 0.49) and 1.7 (95% CI 0.8-3.4, *P*= 0.1) for TPO-Ab positivity, respectively.

Hypoechoic pattern was detected more frequently in patients with ARD or AIRD than in controls (*P*=0.00, *P*=0.00). Although patients with ARD had more frequent hipoechoic pattern than in patients with AIRD, the difference was not statistically significant (*P*=0,08). Compared to other groups the OR for patients with ARD was 15,07 (95% CI 5.9-38.3, *P*=0.00) for hipoechoic pattern. Also the OR for patients with AIRD was 10,7 (95% CI 4.2-27.6, P=0.00) for hipoechoic pattern.

With respect to current treatment, 71 (28.8%) patients with ARD, 75 (35.7%) patients with AIRD, and 5 (4.9%) controls were receiving non-steroidal antiinflammatory agents (NSAIDs); 189 patients (76.5%) with ARD and 67 (31.9%) patients with AIRD were using

**Table 1 .** Demographic features of patients with ARD, AIRD and controls

| | ARD (n=298) | AIRD (n=363) | Controls (n=137) | P |
|---|---|---|---|---|
| **Age. years. mean±SD** | 47.4 ± 11.8 | 42.6 ± 10.7 | 46.4 ± 9.4 | 0.13 |
| **Female/Male. n** | 247/51 | 210/153 | 103/34 | 0.15 |
| **BMI. kg/m$^2$. mean±SD** | 28 ± 4.2 | 26.7 ± 3.9 | 28.5 ± 5.3 | 0.43 |
| **Disease duration. month. mean±SD** | 64 ± 72.8 | 66.5 ± 75.9 | - | 0.5 |

*ARD:* autoimmune rheumatic disese. *AIRD:* autoinflammatory rheumatic disease

**Table 2.** The frequencies of TPO-Ab positivity. HT. and thyroid dysfunction in patients

| | TPO-Ab positivity (F/M) | HT (F/M) | Thyroid dysfunction (F/M) |
|---|---|---|---|
| **Seropositive RA** | 21(33.3)/ 7(43.3) | 23(36.5)/ 7(43.8) | 2(3.2)[a]-5(7.9)[c]/ - |
| **Seronegative RA** | 13(26)/ 6(23.1) | 15(30)/ 8(30.8) | 3(6)[a]-2(4)[c]-2(4)[d]/ 7(26.9)[a] |
| **SLE** | 14(27.5)/ 1(33.3) | 17(33.3)/ 1(33.3) | 5(9.8)[a]-1(2)[b]/- |
| **PSS** | 16(32)/ - | 20(40)/ - | 6(12)[a]-1(2)[c]/- |
| **SSc** | 8(34.8)/ - | 8(34.8)/- | 2(8.7)[b]-1(4.3)[d]/- |
| **PM** | 2(50)/ 1(50) | 2(50)/ 1(50) | 1(25)[a]/- |
| **DM** | 1(100)/- | 1(100)/- | -/- |
| **MCTD** | 2(40)/- | 2(40)/- | 2(40)[c]/- |
| **FMF** | 4(15.4)/ 1(14.3) | 4(15.4)/ 1(14.3) | 3(11.5)[a]/- |
| **Behcet's disease** | 9(22)/- | 10(24.4)/- | 6(14.6)[a]-2(4.9)[c]/ 1(4.3)[a] |
| **Gout** | 2(14.3)/ 2(16.7) | 2(14.3)/ 2(16.7) | 1(7.1)[a]/ 2(16.7)[a] |
| **AS** | 11(23.3)/ 11(17.2) | 13(27.7)/ 12 (18.8) | 2(4.3)[a]-2(4.3)[b]-1(2.1)[c]/ 2(3.1)[a]-1(1.6)[b]-4(6.3)[c] |
| **ReA** | 1(16.7)/ 1(10) | 1(16.7)/ 1(10) | 1(16.7)[a]/ 2(7.4)[a]-2(7.4)[c] |
| **EA** | 1(33.3)/ 1(33.3) | 1(33.3)/ 1(33.3) | -/- |
| **PsA** | 21(30.4)/ 2(7.4) | 23(33.3)/ 3(11.1) | 5(7.2)[a]-1(1.4)[b]-2(2.9)[c]/- |
| **AOSD** | - /2(28.6) | -/ 2(28.6) | -/ 2(28.6)[d] |

*HT:* Hashimoto's thyroiditis. *RA:* Rheumatoid arthritis. *SLE:* Systemic Lupus Eritematozus. *PSS:* Primary Sjogren's Syndrome *PM:* Polymyositis. *DM:* Dermathomyositis. *ANCA:* Anti neutrophilic cytoplasmic antibody. *MCTD:*Mixed connective tissue disease.*FMF:* Familial Meditarrenian Fever. *AS:* Ankylosing spondylitis. *ReA:* Reactive Arthtritis. *EA:* Entheropatic arthtiritis. *PsA:* Psoriatic Arthtiritis. *AOSD:* Adult Onset Still Disease. *F:* Female. *M:* Male
*a:* subclinical hypothyroidism
*b:* hypothyroidism
*c:* subclinical hyperthyroidism
*d:* hypothyroidism

steroid. Receiving NSAIDs was more frequent in patients those having than not having HT (ARD; *P*=0.00, AIRD; *P*=0.01, controls; *P*=0.00) also using steroid was more frequent in patients with ARD those having than not having HT (*P*= 0.021).

The patients with ARD and AIRD were receiving DMARD (205, 83% and 158, 75.2%) or biological agents (15, 6.1% and 40, 19.1%). There was no difference in HT frequency between the patients using DMARD and the patients using biologic agents (ARD: *P*=0.75, AIRD: *P*=0.57). Furthermore mean TPO-Ab levels were lower in patients with ARD those receiving biologic agents than receiving DMARD while the difference was not statistically significant (*P*=0.67) also in AIRD group no relationship was found in serum TPO-Ab levels (*P*=0.63).

Thyroid nodule was discovered in 97 patients with ARD, 75 patients with AIRD and 28 controls. There was no meaningful difference in thyroid nodule frequency among groups (*P*=0.23). Fine needle aspiration biopsy (FNAB) findings of 29 patients with ARD, 21 patients with AIRD and 2 controls for thyroid nodule were reported as benign cytology. Comparison of thyroid echogenity and laboratory findings among females is shown in Table 3.

*Results in Males:* Subclinical hyperthyroidism was found in 7 (13.7%) patients with ARD. In AIRD group, subclinical hypothyroidism in 7 (4.6%), hypothyroidism in 1 (0.7%), subclinical hyperthyroidism in 6 (3.9%), and hyperthyroidism in 2 (1.3%) patients were detected. 3 (17.6%) patients with subclinical hyperthyroidism meets the criteria for HT in ARD group. Furthermore only one

**Table 3.** Comparison of thyroid echogenity and laboratory findings among females

| | ARD (n=247) | AIRD(n=210) | Controls(n=103) | P |
|---|---|---|---|---|
| **TSH. µU/ml** | 2.1±2.5 | 2.1±2 | 1.6±1.1 | 0.109 |
| **fT3. pmol/L** | 4.3±0.7 | 4.4±0.8 | 4.5±0.7 | 0.134 |
| **fT4. pmol/L** | 12.9±2.3 | 12.9±2.3 | 12.2±1.3 | **0.021** |
| **TPO-Ab. IU/ml** | 72.7±207 | 80.6±245.7 | 1.1±2.4 | **0.003** |
| **TG-Ab. IU/ml** | 46.1±127.4 | 34.7±108.4 | 3.5±10.6 | **0.004** |
| **ESH** | 27.9±16.1 | 21.7±12.6 | 20.6±8.8 | **0.000** |
| **CRP** | 4.9±5 | 4.4±4.3 | 3±2.3 | **0.000** |
| **TPO-Ab positive** | 77(31.2) | 49(23.3) | 2(1.9) | **0.000** |
| **TG-Ab positive** | 85(34.4) | 56(26.7) | 4(3.8) | **0.000** |
| **Hypoechoic pattern** | 108(43.7) | 75(35.7) | 5(4.9) | **0.000** |
| **Hashimoto's thyroiditis** | 88(35.6) | 54(25.7) | 2(1.9) | **0.000** |

*ARD:* autoimmune rheumatic disese. *AIRD:* autoinflammatory rheumatic disease

patient (4.5%) with hypothroidism was diagnosed also HT in AIRD group. Among groups no significant difference was found in thyroid dysfunction (*P*=0.104), in addition no relationship between disease duration, BMI or age and thyroid dysfunction was established (*P*=0.6, *P*=0.045, *P*=0.805, respectively).

No difference was found in serum TSH, fT3, and fT4 values among groups (data is shown in Table 4). TPO-Ab levels were significantly higher in patients with ARD compare to the controls (*P*=0.048). Furthermore in patients with ARD mean TPO-Ab values were significantly higher than in patients with AIRD (*P*=0.014). The patients with ARD had more frequent TPO-Ab positivity than controls (*P*=0.023), also the patients in ARD group had more frequent TPO-Ab positivity than the patients in AIRD group (*P*=0.007). There was no difference in prevalence of TPO-Ab positivity between AIRD and controls (*P*=0.49). There was no correlation between the patients with hypothyroidism and serum TPO-Ab-positivity, among groups (*P*=0.181).

HT was significantly more frequent in patients with ARD than in controls and also than in patients with AIRD (*P*=0.09, *P*=0.003). Compared to patients with AIRD and controls, the OR for patients with ARD was 5,1 (95% CI 1.3-19.3, *P*= 0.015) for HT frequency. Moreover the OR for patients with AIRD was 1,7 (95% CI 0.4-6.1, *P*= 0.39) for HT frequency. There was no relationship in age or BMI between the patients with having and those not having HT in ARD or AIRD groups (*P*=0.42, *P*=0.11 and *P*=0.13, 0.52).

In patients with ARD with a disease duration ≤ 2 years had a higher prevalence of HT and TPO-Ab positivity than in patients with a disease duration > 2 years (*P*=0.006, *P*=0.001). In multivariable analysis, the ORs for patients with ARD and AIRD those disease duration ≤ 2 years compared to those disease duration > 2 years were 5,5 (95% CI 1.5-19.7, *P*=0.009) and 1,07 (95% CI 0.3-2.9, *P*= 0.8) for HT frequency, respectively. In addition the OR for patients with ARD those disease duration ≤ 2 years compared to those disease duration > 2 years was 8,2 (95% CI 2.1-32, *P*=0.02) for TPO-Ab positivity and the OR for patients with AIRD was 1,2 (95% CI 0.4-3.5, *P*=0.67) for TPO-Ab positivity.

There was no difference in hypoechoic pattern among groups (*P*=0.091). Although patients with ARD have more frequent hipoechoic pattern than AIRD, the difference was not statistically significant (*P*=0.072).

With respect to current treatment, 17 (33.3%) patients with ARD, 52 (34%) patients with AIRD and, 1 (2.9%) participant in control group were receiving NSAIDs; 38 patients (74.5%) with ARD and 29 (19%) patients with AIRD were using steroid. HT was more frequent in patients with AIRD and in controls those receiving than not receiving NSAIDs (*P*=0.00, *P*=0.001 respectively). No significant difference was found in HT frequency between patients those receiving and not receving NSAIDs also between patients those using and not using steroid in ARD group (*P*=0.25, *P*=0.92 respectively).

The patients were receiving DMARDs (30, 58.8% and 95, 62%) or biological agents (2, 3.9% and 48, 31.4%) in ARD and AIRD group. There was no difference in HT frequency between those receiving DMARDs and biologic agents in patients with ARD or AIRD (*P*=0.32, *P*=0.14). While the patients in ARD group who were receiving biologics had lower mean TPO-Ab levels than those receiving DMARDs, the diffence was not significant (*P*=0.8). No relationship was found in serum TPO-Ab levels in patients with AIRD between patients who were receiving DMARDs and biologic agents (*P*=0.28).

Thyroid nodule was discovered in 18 patients with ARD, 50 patients with AIRD and in 8 controls. There was no meaningful difference in thyroid nodule frequency among groups (*P*=0.24). FNAB findings of 6 patients with ARD, 10 patients with AIRD and 4 controls for thyroid nodule were reported as benign cytology. FNAB finding of one patient with ARD was reported as malignant cytology and when this patient was operated, the result was compatible with papillary microcarcinoma.

**Table 4.** Comparison of thyroid echogenity and laboratory findings among males

| | ARD (n=51) | AIRD(n=153) | Controls(n=34) | P |
|---|---|---|---|---|
| **TSH. µU/ml** | 1.03±0.5 | 1.4±1.4 | 1.2±1.2 | 0.083 |
| **fT3. pmol/L** | 4.3±1.2 | 4.6±0.8 | 4.8±0.7 | 0.051 |
| **fT4. pmol/L** | 12.7±1.7 | 13.3±2.1 | 12.5±1 | 0.066 |
| **TPO-Ab. IU/ml** | 72.7±207 | 13.6±49.5 | 8.9±28.6 | **0.012** |
| **TG-Ab. IU/ml** | 44.8±117.6 | 9.2±32.3 | 15±66.7 | 0.157 |
| **ESH** | 24.3±70.8 | 16.3±12.3 | 11.5±4.7 | **0.000** |
| **CRP** | 29.4±22.6 | 4.1±4.1 | 1.9±0.8 | **0.000** |
| **TPO-Ab positive** | 15(29.4) | 20(13.1) | 3(8.8) | **0.000** |
| **TG-Ab positive** | 18(35.3) | 22(14.4) | 3(8.8) | **0.000** |
| **Hypoechoic pattern** | 17(33.7) | 32(20.9) | 5(14.7) | 0.091 |
| **Hashimoto's thyroiditis** | 17(33.3) | 22(12.4) | 3(8.8) | **0.003** |

*ARD:* autoimmune rheumatic disese. *AIRD:* autoinflammatory rheumatic disease

Furthermore it was noted that he was treated with total thyroidectomy and levothyroxin suppressive treatment. Comparison of thyroid echogenity and laboratory findings among males is shown in Table 4.

## DISCUSSION

Many rheumatic diseases have been reported to be associated with HT. Bianchi et al. 1993 investigated the frequency of thyroid involvement in rheumatic diseases such as RA, PsA and AS also in healthy male controls. The frequency of TPO-Ab positivity was found to be significantly higher only in RA and PsA patient groups, but not in AS group, compared to healthy controls. They confessed that the number of patients with AS in this study was quite limited to draw a firm conclusion (Bianchi et al., 1993). Innocencio *et al*. 2003 reported 32% and 4% positivity rates of TG-Ab and TPO-Ab in patients with SSc and RA, respectively. El-Sherif *et al*. 2003reported an increase in thyroid disorders in patients with RA and/or SLE. Moreover Scofield 1995, indicated there was no greater risk of HT in patients with SLE. D'Arbonneau *et al*. 2003 found a significant difference in patients with PSS had HT comparing to controls.

Taken together, these previous studies showed that HT was slightly increased in the whole group of ARD patients. However, the data is more confusing for AIRD. Triantafillidis *et al*. 1990 reported that HT is an extraintestinal complication of inflammatory bowel disease, and the increased prevalence of thyroid antibodies in patients with ulcerative colitis. While Bianchi *et al.* 1993 and Peluso *et al.* 2011 could not show significantly increased frequency of HT in patients with AS, Lange *et al.* 1999 reported significantly increased evidence of HT in a small number of female patients with AS compared to age-matched healthy females. Despite the lack of comparison with a healthy control group, Tarhan *et al*. 2013 concluded that frequency of HT was higher in the whole group of AS patients than reported in the literature. There is also a study investigating the prevalence of HT and hypothyroidism in PsA, which is another subgroup of SpA. They observed a significantly higher prevalence of HT in men and women with PsA and of clinical hypothyroidism in women with PsA as compared to the general population (Antonelli et al., 2006). Dikbas *et al*. 2013 investigated the HT in patients with FMF. Although the difference was not statistically significant, thyroid autoimmunity was observed more frequently in patients with FMF than in healthy controls, and thyroid autoantibodies were significantly higher in patients with FMF.

The association between autoimmune and autoinflammatory rheumatic disorders and HT have been suggesting the presence of common environmental and genetic factors, with similar pathogenic mechanisms. For instance, Punzi *et al.* 2004 reported the participation of the histocompatibility antigens (HLA) of the haplotypes HLA-B8 and DR3 in both HT and PSS, because of the high frequency of those haplotypes in Caucasian patients with those diseases. In addition it was suggested that HLA-B27 positivity may also have an additional role in the pathogenesis of HT, also another molecule known as cytotoxic T-lymphocyte antigen 4 (CTLA-4) was reported to play a role in the pathogenesis of both AS and HT (Lee et al., 2010). Molteni *et al*. 1997 reported that TPO-Ab and TG-Ab positivity and the genetic association with HLA class II antigens in patients with scleroderma. Individuals with TPO-Ab had a higher frequency of the HLA-DR15 allele than patients without those antibodies, suggesting that the HLA-DR15 allele can be a marker of immunogenicity for the formation of TPO-Ab.

Another point deserving attention is gender differences. HT is 15–20 times as frequent in women as in men (Tunbridge et al., 1977). In current study much of the significant differences with respect to parameters reflecting HT were mainly driven by the differences between female and male patients, also these

differences was seen in ARD group mostly. In female patients with ARD or AIRD mean TPO-Ab levels, TPO-Ab positivity, HT frequency, and hypoechoic pattern were significantly higher than controls. In male patients with ARD mean TPO-Ab levels, TPO-Ab positivity, HT frequency, and hypoechoic pattern were higher than controls. In both female and male population, TPO-Ab levels, TPO-Ab positivity, Furthermore HT frequency, and hypoechoic pattern were higher in patients with ARD than in patients with AIRD. We found no relationship between age and HT frequency in patients with ARD or AIRD. Additionally TPO-Ab positive female patients had much higher prevelance of hypothyroidism comparing to male patients among ARD or AIRD groups. These results suggest that female gender and having an ARD have an important role for thyroid autoimmunity.

Antonelli *et al.* 2006 observed that the frequency of thyroid disorders was significantly lower in the subgroup of patients receiving anti-TNF treatment. In another study, the patients with RA were treated with adalimumab for 6 months, and it was discovered that anti-TNF treatment had ameliorated the thyroid dysfunction in hypothyroid patients (Raterman et al., 2011). According to the results of our study HT were discovered similar those receiving biological agents with those receiving traditional DMARDs in ARD or AIRD groups. When the data was investigated regarding gender, mean TPO-Ab levels were lower in female patients with ARD or AIRD who were receiving biologic agents than receiving DMARDs. This finding may be the result of the role of TNF-α in the pathogenesis of HT.

Ott *et al*. 2011 reported that women with HT having high TPO-Ab titers suffer from a high symptom load such as chronic weakness, fatigue, and irritability, as well as decreased quality of life, regardless of hypothyroidism. Bazzichi *et al.* 2012 showed that HT patients had higher incidence of clinical symptoms and significantly higher values of fibromyalgia impact questionnaire (FIQ), visual analog scale (VAS) pain and VAS fatigue with respect to patients affected by subclinical hypothyroidism. Tension, headache, muscle spasm and affective disorders, even if not reaching the statistical significance, resulted in higher percentage in HT patients with FM comorbidity with respect to subclinical hypothyroidism. Mader *et al.* 2007 reported the degree of disease activity did not correlate with TSH, fT4, TG-Ab or TPO-Ab levels in patients with SLE. Koszarny *et al*. 2013 found that there were significant differences in the mean disease activity score (DAS) 28 between TPO-Ab-positive and TPO-Ab-negative groups. We noted that in females, the patients or controls and in males, the patients with AIRD or controls had much higher frequency of HT those using than those not using NSAIDs. In addition while no difference was found among males, in females we showed that patients with ARD had HT more frequently those receiving steroid comparing to those not receiving. Although we didn't review disease activity or FIQ and VAS values of the patients, the possible reason for these results may be derived from patients high disease activity and fibromylagia symptoms concomitant with HT.

The study of Peluso *et al.* 2011, in the whole group and subgroups of SpA (excluding AS) HT significantly more frequent in SpA patients with longer disease duration. In addition Marrasini *et al*. 2007, observed no correlation between disease duration or age with thyroid dysfunction in patients with SSc. In present study we showed that disease duration, BMI and age had no impact on thyroid dysfunction in patients with ARD or AIRD. In our ARD and AIRD groups, subclinical hypothyroidism was discovered in 17 (17 female) %6.3 and 25 (18 female/7 male) patients 3.4%, overt hypothyroidism in 4 (4 female) 1.3 % and 4 (3 female/1 male) 0.4 %, subclinical hyperthyroidism in 17(10 female/7 male) 2.7% and 11(5 female/6 male) patients 5.5% and overt hyperthyroidism in 3 (3 female) 0.5% and 2 patients (2 male) 0.8%. Only hypothyroidism was in relationship with HT in female patients with ARD and also male patients with AIRD. In our experience, TPO-Ab positivity occurs more frequently in patients with a short disease duration (≤ 2 years) in ARD patients, this suggests a possible relationship between the reduction of the inflammatory process by receiving steroid.

However, strikingly low frequency of HT in controls, might have also contributed to significant differences between the ARD or AIRD and control groups. In order to better clarify the issue of whether HT is really significantly associated with ARD or AIRD, further prospective controlled studies with better elucidation of the underlying pathogenic mechanisms for both diseases are required. In addition we recognize the limitation of this study is that we did not have doppler ultrasonographic examination of the thyroid because the present study is a retrospective study. It could be interpreted better if the presence of thyroid dysfunction could have been demonstrated before and after biologic treatment, and the impact of biologic treatment on thyroid function could be shown more precisely.

In conclusion because of the high prevalence of HT particularly in female patients with ARD and AIRD and also in male patients with ARD, it is clinically important to screen patients with ARD or AIRD for the presence of thyroid autoimmunity or thyroid dysfunction.

## Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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## Informed consent

Informed consent was obtained from all individual participants included in the study.

## Contribition of authors

This work was carried out in collaboration between all authors. Authors SA and IT wrote the draft of the manuscript. Authors SA designed the study and acquired the data. Authors SA and MSU analysed data. Authors HH and SA managed literature searches and contributed to the correction of the draft. All authors read and approved the final manuscript.

## Conflict of Interest

All authors declares that they have no conflict of interest.

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