ORIGINAL RESEARCH PAPER

Volume-7 | Issue-8 | August-2018 | PRINT ISSN No 2277 - 8179

INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

THE PREVALENCE OF THYROID DYSFUNCTION IN RHEUMATOID ARTHRITIS AND ITS CORRELATION WITH DISEASE ACTIVITY

Medicine

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ABSTRACT

The relationship between thyroid dysfunction and rheumatoid arthritis (RA) has been a subject of considerable discussion. So the Aim of study was to determine the prevalence of thyroid dysfunction in patients with RA and if there is correlation with disease activity or not. A total of 100 RA patients and 65 control participants were enrolled in this cross sectional prospective study. RA patients were subjected to full clinical evaluation including medical and rheumatological history and examination. Disease activity was measured by using Clinical Disease Activity Index (CDAI). Patients and controls underwent thyroid function test and erythrocyte sedimentation rate (ESR). Rheumatoid factor (RF) and Anti-citrullinated protein antibody (ACPA) were recorded for the patients. The mean age of the studied groups was 46.62 ± 12.6 years and 46.69 ± 13.3 years in RA and control groups, respectively. Statistically, there is no significant difference between both groups in age, gender distribution, and body mass index (BMI). Clinical hypothyroidism was reported in 21 (21.0%) of patients group while it was in 1 (1.5%) of controls group, clinical hyperthyroidism was in 1 (1.0%) of patients group whereas no one in controls group, and subclinical hypothyroidism was reported in 7 (7.0%) of patients group while it was only in 3 (4.6%) of controls group. There is no statistically significant association between thyroid dysfunction and disease activity measured by (CDAI). Thyroid dysfunction was more frequent in RA patients in comparison to healthy populations and hypothyroidism was the more frequent type. There is no correlation between thyroid dysfunction and RA disease activity.

KEYWORDS

rheumatoid arthritis, thyroid dysfunction, correlation, hypothyroidism, hyperthyroidism

INTRODUCTION

Rheumatoid arthritis is a systemic autoimmune disease with variable manifestations. The primary expression of the disease occurs in the synovial tissues, and is characterized by symmetric polyarticular inflammation, which can lead to progressive joint damage [1]. The incidence of RA is estimated that to be 1% in most developed countries [2], Females are two to four times more frequently affected than the males and the disease incidence increases with age and plateaus around 60 years [3]. Extra-Articular manifestations occur in up to 50% in patients with RA and generally indicate a poor prognosis, including increased morbidity and mortality [4]. The patients diagnosed to have RA according to the 2010 American College of Rheumatology (ACR)/EULAR RA classification criteria [5]. Previously the patients classified as RA when they satisfy the 1987 ACR rheumatoid arthritis classification criteria. [6]. The thyroid consists of two lobes connected by an isthmus. It is located anterior to the trachea between the cricoid cartilage and the suprasternal notch. The normal thyroid is 12–20 g in size, highly vascular, and soft in consistency, produces two related hormones, thyroxine (T4) and triiodothyronine (T3) [7]. Thyroid hormone biosynthesis and secretion are maintained within narrow limits by a regulatory mechanism that is very sensitive to small changes in circulating hormone concentrations [8,9]. Thyrotropin-releasing hormone (TRH) is synthesized by the hypothalamus and is transported to the pituitary gland, stimulating the synthesis and secretion of thyroid-stimulating hormone (TSH) [7,10]. Thyroid hormones act via negative feedback predominantly through thyroid hormone receptor β2 (TRβ2) to inhibit TRH and TSH production [7, 11]. When the levels of thyroid hormone reduce, this leads to increase basal TSH production and enhance TRH-mediated stimulation of TSH. High levels of thyroid hormone cause rapid and direct suppression of TSH secretion and inhibit TRH stimulation of TSH [7,12]. When patients' thyroid hormone levels remain within broad reference ranges, and TSH levels become abnormal, these conditions termed *subclinical hypothyroidism* and *subclinical thyrotoxicosis* [13]. Moreover, Thyroid dysfunction can be broadly classified as hypothyroidism and hyperthyroidism [14]. A low free T4 level in conjunction with a persistently elevated TSH level represents overt primary hypothyroidism [11], whereas a normal free T4 level with an elevated TSH level is termed subclinical hypothyroidism [15]. Overt thyrotoxicosis is characterized by free T4 or T3 elevation, whereas subclinical thyrotoxicosis is characterized by a suppressed TSH level with free T4 and T3 levels within the normal reference range [11]. The relationship between abnormal thyroid function and RA have been a subject of discussion [16]. While some studies reported a higher incidence of thyroid disorders in patients with RA [17], others did not record such association [18, 19]. Other studies showed that abnormal thyroid status might trigger or exacerbate musculoskeletal disease [20].

Many patients diagnosed having RA initially, develop thyroid disorders later on. The opposite is also observed, i.e. musculoskeletal disorders, including RA is known to develop in patients with various thyroid disorders [21]. In addition, there was a more recent study in which thyroid dysfunction and/or autoimmune thyroid disease (AITD) was detected in 6-33.3% of patients with RA, which can be due to the natural feature of autoimmune disease and their tendency to overlap [22].

PATIENTS AND METHODS

A cross sectional prospective study was conducted at the Rheumatology Unit of Baghdad Teaching Hospital / Medical City from November 2016 to November 2017.

A total of 100 patients aged > 16 years, diagnosed to have RA according to the 2010 American College of Rheumatology (ACR)/EULAR RA classification criteria [5], or had been diagnosed previously according to the ACR revised criteria of RA 1987 [6], were included in the study and compared with another 65 healthy controls matched in age and sex.

Patients were excluded from the study if they had one or more of the following:

1) Patients with history of thyroid disease or who had undergone thyroidectomy.
2) Patients on medications known to cause thyroid dysfunction (e.g., Amiodarone, Lithium, Interferon alpha, Aminoglutethimide Carbamazepine, Furosemide, Phenytoin, and others) [7, 11] and radiotherapy.
3) Any collagen disease other than RA.
4) Concurrent severe infection.
5) Patients with chronic liver or renal diseases.
6) Evidence of malignancy.
7) Pregnant women and postpartum women for one year.
8) Patients with diabetes mellitus.

All patients were asked for age, sex, disease duration, and smoking status. We measured height in centimeter and weight in kilogram and calculate the body mass index (BMI) according the equation BMI = weight / height^2. Disease activity and medications (Methotrexate, Azathioprine, Hydroxychloroquine, Leflunomide, Sulfasalazine, and biological treatment) were recorded. All controls were asked for age, sex, smoking status, height, weight and BMI.

All the patients were subjected to a clinical evaluation, which included detailed medical and rheumatological history and a careful general, musculoskeletal and thyroid gland examination. Disease activity was

assessed using clinical disease activity index (CDAI) including 28 tender and swollen joint count scores, patient global assessment of disease activity and physician global assessment of disease activity [23,24]. The activity score of the patients is graded as follows:

a) Remission CDAI ≤ 2.8
b) Low disease activity CDAI > 2.8 and ≤ 10
c) Moderate disease activity CDAI > 10 and ≤ 22
d) High disease activity CDAI > 22

Five milliliters of venous blood samples were taken in red tube contain EDTA in both groups for measuring erythrocyte sedimentation rate (ESR) and thyroid function test which include: Thyroid stimulating hormone (TSH), Free serum triiodothyronine (FT3) and Free serum thyroxine level (FT4) were measured by using bioactiva enzyme-linked immunosorbent assay (ELISA) kits (bioactiva diagnostic GmbH, Louisenstr. 137, D-61348 Bad Homburg, Germany). The normal physiological range in serum (as listed in the manufacturer's brochure) were: TSH= 0.4-4.2µIU/ml, Free T3 = 1.4-4.2pg/ml, Free T4= 0.8-2.0 ng/dl. RF and ACPA were recorded for the patients.

Clinical hypothyroidism and hyperthyroidism were defined according to the criteria of thyroid abnormalities as defined by the Dutch National Healthcare consensus committee[25].

- Subclinical hypothyroidism: it was characterized by increased serum TSH level and normal serum FT4 level.
- Clinical hypothyroidism: it was characterized by increased serum TSH level and decreased serum Ft4.
- Subclinical hyperthyroidism: it was characterized by normal serum FT4 and FT3, with TSH levels below the normal range.
- Clinical hyperthyroidism: it was characterized by increased serum FT4 and FT3, with TSH levels decreased below normal range.

Informed consent was obtained from each participant in this study, and the study was approved by the supervising committee of the Iraqi Board of Medical Specializations.

Statistical analysis:
Statistical package for social sciences (SPSS) version 20 was used for data entry and analysis. Frequency and percentage was used to represent the categorical data, mean and standard deviation for numerical data. Independent student T-test and chi-square (Fischer exact test if not applicable) test was used to confirm significance and $p<0.05$ was considered significant.

RESULTS

The findings of the current study showed there was no significant difference for mean age or BMI between studied groups ($p>0.05$) as well as the results of gender distribution, marital and smoking status, revealed there was no significant association between studied groups ($p>0.05$) as seen in table 1.

TABLE. -1 SOCIODEMOGRAPHIC CHARACTERISTICS OF STUDY GROUPS

		groups				p-value
		Patients	(N=100)	Controls	(N=65)	
		mean	SD	mean	SD	
Age (years)		46.62	12.6	46.69	13.3	0.9
BMI (kg/m^2)		28.7	5.6	27.5	1.7	0.1
		No.	%	No.	%	
Gender	Female	86	86.0%	55	84.6%	0.4
	Male	14	14.0%	10	15.4%	
Marital status	married	83	83.0%	54	83.1%	0.9
	single	17	17.0%	11	16.9%	
Smoking	Non	91	91.0%	58	89.2%	0.8
	smoking	6	6.0%	5	7.7%	
	x-smoker	3	3.0%	2	3.1%	

BMI: body mass index, SD: standard deviation

The mean duration of disease was 9.3±7.3 years, mean CDAI was 17.5±7.3, 23% showed high activity, 63% with RF positive, 31% with ACPA positive, 92% on Etanercept and the majority 59% on Methotrexate agent as displaced in table 2.

TABLE-2. CLINICAL CHARACTERISTICS OF PATIENTS GROUP

Variables		Mean	Std. Deviation
Disease duration (years)		9.3	7.3
CDAI		17.5	7.3
		No.	%
Activity	high activity	23	23.0%
	low activity	15	15.0%
	moderate activity	62	62.0%
RF (IU/mL)	Negative	37	37.0%
	Positive	63	63.0%
ACPA(U/mL)	Negative	69	69.0%
	Positive	31	31.0%
Biological	Etanercept	92	92.0%
	Rituximab	4	4.0%
	Without biological	4	4.0%
DMARD	MTX	59	59.0%
	Without DMARD	23	23.0%
	Azathioprine	7	7.0%
	HCQ	5	5.0%
	HCQ + MTX	2	2.0%
	Azathioprine + Sulfasalazine	1	1.0%
	Leflunomide	1	1.0%
	MTX + sulfasalazine	1	1.0%
	Sulfasalazine	1	1.0%

ACPA: anti-citrullinated protein antibody, CDAI: clinical disease activity index, DMARD: disease modifying anti-rheumatic drugs, HCQ: hydroxychloroquine, MTX: methotrexate, RF: rheumatic factor
The mean value of ESR of patients group was significantly higher than the controls group (36.5, 9.7) respectively, ($p=0.01$). The mean value of FT3 and FT4 of patients group (1.9, 0.9 respectively) was significantly ($p=0.01$) lower than the controls group (3.6, 1.2 respectively). For TSH level, the results showed there was no significant difference ($p=0.9$) in mean value of TSH even that the mean value of patients group was higher than that of controls group but it did not reach the significant level as seen in table 3.

TABLE -3 MEAN OF ESR, FT3, FT4 AND TSH OF STUDIED GROUPS

	Groups				P-value
	Patients		Controls		
	Mean	Std. Deviation	Mean	Std. Deviation	
ESR (mm/hr.)	36.5	23.1	9.7	2.7	0.01
FT3 (pg./ml)	1.9	1.0	3.6	0.5	0.01
FT4 (ng/dl)	0.9	0.3	1.2	0.3	0.01
TSH (µIU/ml)	4.2	6.2	3.02	2.3	0.9

ESR: erythrocyte sedimentation rate, FT3: free triiodothyronine, FT4: free thyroxine. Std. deviation: standard deviation, TSH: thyroid-stimulating hormone.

The incidence of hypothyroid status was reported in 21 patients of patients group while it was reported in one subject of controls group in addition the incidence of subclinical hypothyroid status and hyperthyroidism also were higher with patients group in comparison to controls group and the overall all association was significant($p=0.02$) as seen in table 4.

TABLE-4 ASSOCIATION OF THYROID STATUS RESULT AND STUDIED GROUPS

Results	Groups			P-value
	Patients (N=100)	Controls (N=65)	Total (N=165)	
Hyperthyroidism no. (%)	1 (1.0%)	0 (0.0%)	1 (0.6%)	0.02
Hypothyroidism no. (%)	21(21.0%)	1 (1.5%)	22 (13.3%)	
Normal no.(%)	71 (71.0%)	61(93.9%)	132 (80.0%)	
Sub clinical Hypothyroidism no. (%)	7 (7.0%)	3 (4.6%)	10 (6.1%)	

There was a direct correlation between ESR and each of CDAI, FT3, FT4 and TSH level, but the significant correlation was reported between ESR and CDAI as well as between ESR and FT3 ($P<0.05$). Insignificant inverse correlation was seen between CDAI and each of FT3 and FT4 but significant inverse correlation was reported between TSH and each of FT3 and FT4 as seen in table 5.

TABLE-5 CORRELATION OF PARAMETERS OF STUDIED GROUPS

Correlations						
		ESR	CDAI	F T3	F T4	TSH
ESR	Pearson Correlation	1	0.289**	0.245*	0.030	0.009
	p-value		0.004	0.014	0.766	0.933
CDAI	Pearson Correlation	0.289**	1	-0.058	-0.126	0.172
	p-value	0.004		0.569	0.212	0.088
FT3	Pearson Correlation	0.245*	-0.058	1	0.255*	-0.221*
	p-value	0.014	0.569		0.010	0.027
FT4	Pearson Correlation	0.030	-0.126	0.255*	1	-0.226*
	p-value	0.766	0.212	0.010		0.024
TSH	Pearson Correlation	0.009	0.172	-0.221*	-0.226*	1
	p-value	0.933	0.088	0.027	0.024	

CDAI: clinical disease activity index, ESR: erythrocyte sedimentation rate FT3: free triiodothyronine, FT4: free thyroxine, TSH: thyroid-stimulating hormone.

The results indicated there was no significant association between the activity of disease and thyroid status even that the incidence of hyperthyroid, hypothyroid and subclinical hypothyroid status was reported higher with patients of moderate activity status but the difference did not reach the significant level(p=0.5) as showed in table 6.

TABLE-6 ASSOCIATION BETWEEN THE ACTIVITY OF DISEASE AND THYROID STATUS

Results	Activity status (CDAI)			P-value
	High Activity (N=23)	Moderate Activity (N=62)	Low Activity (N=15)	
Hyperthyroidism no. (%)	0 (0.0%)	1 (1.6%)	0 (0.0%)	0.5
Hypothyroidism no. (%)	8 (34.8%)	10 (16.1%)	3 (20.0%)	
Normal no. (%)	14 (60.9%)	47 (75.8%)	10 (66.7%)	
Sub clinical Hypothyroidism no. (%)	1 (4.3%)	4 (6.5%)	2 (13.3%)	

CDAI: clinical disease activity index.

The results showed that the hypothyroid status was reported in 20 patients of RF positive status in comparison to only one patient of RF negative status in addition the incidence of subclinical hypothyroid and hyperthyroid status was higher with patients of RF positive status and this association was statistically significant(p=0.01) as seen in table 7.

TABLE -7 ASSOCIATION OF RF AND THYROID STATUS

Results	RF status		P-value
	Positive (N=63)	Negative (N=37)	
Hyperthyroidism no. (%)	1 (1.6%)	0 (0.0%)	0.01
Hypothyroidism no. (%)	20 (31.7%)	1 (2.7%)	
Normal no. (%)	35 (55.6%)	36 (97.3%)	
Sub clinical Hypothyroidism no. (%)	7 (11.1%)	0 (0.0%)	

RF: rheumatic factor

The results showed that the incidence of hypothyroid, subclinical hypothyroid and hyperthyroid status was higher with negative status of ACPA but this difference did not reach the significant level (p=0.2) as seen in table 8.

TABLE-8 ASSOCIATION OF ACPA AND THYROID STATUS

Results	ACPA status		P-value
	Positive (N=31)	Negative (N=69)	
Hyperthyroidism no. (%)	0 (0.0%)	1 (1.4%)	0.2
Hypothyroidism no. (%)	10 (32.3%)	11 (15.9%)	
Normal no.(%)	19 (61.3%)	52 (75.4%)	
Sub clinical Hypothyroidism no. (%)	2 (6.4%)	5 (7.3%)	

ACPA: anti-citrullinated protein antibody

DISCUSSION

There are increasingly recognized associations between RA and other medical conditions, one of these are thyroid disorders. The association between RA and the thyroid disorders has been studied with conflicting results. Some studies have suggested that the performance of thyroid function tests in patients with RA as a part of biochemical and immunological profiles may help in early detection of associated thyroid disorders[16].

The gender distribution in current study was 86% of RA patients group were females, these results were consistent with other studies such as *Kvein et al.* [17] and *Del Rincón et al.* [28] that found a predominance of female gender in RA. There was no statistically significant difference between RA group and controls in age and BMI.

This study showed that there is a significant association between thyroid dysfunction and RA, as it present in 29 (29.0%) of RA patients and 4 (6.1%) of control participants. The current study is in agreement with the study of *Elattar et al.* [14], who found higher prevalence of thyroid dysfunction in RA patients, as thyroid abnormalities were present in (29.3%) of RA patients and (8%) of control participants and the study of *Shiroky et al.* [29] who found that (30%) of RA patients had evidence of thyroid dysfunction compared with (11%) of their controls. The study of *Mousa A et al.* [30] also found that thyroid dysfunction occurs in patients with RA at a much higher frequency than comparable controls. But the results of this study was inconsistent with the study of *Siddhartha Kumar et al.*[31] who found no statistically significant difference observed in the prevalence of thyroid disorders between the two groups, as the overall thyroid dysfunction was (35.2%) in RA group while in controls was (22.2%). Other studies such *Marasini B et al.* [18] and *McCoy SS et al.* [19], did not document a significant difference in the prevalence of thyroid disorders in patients and controls groups. The cause of inconsistency may be due to the fact that most of these studies used a relatively small sample size, which limited their power to detect whether there is an association between RA and thyroid dysfunction is present, and also may be due to lack of consistent criteria for categorization thyroid function between different countries[26,32].

Hypothyroidism was the most common type of thyroid dysfunction in our study, found in 21 (21.0%) of RA patients (table 4). This result is consistent with *Unnikrishnan AG, et al.* [33] who found that the hypothyroidism is the most common thyroid disorder associated with RA, which is about 3.5 times greater than the reported prevalence of hypothyroidism in the controls. *Elattar et al.*[14] study showed the same result of this study regarding the prevalence of hypothyroidism. Although several studies confirmed the significant prevalence of hypothyroidism in RA[29,30], the Rochester epidemiology project found no significant difference in the prevalence of hypothyroidism in RA patients [19]. The prevalence of hypothyroidism in RA patients may be due to several factors one of them is the drugs that are used in RA such as NSAID and corticosteroids, which have been shown to alter thyroid gland function [29, 34]. The anti-thyroid activity of one of the antibodies produced in RA may be one of the causes for development of hypothyroidism in RA patients[35]. Genetic predisposition identified by a certain Human Leucocyte Antigen (HLA), most commonly HLA-DR type, is one possible explanation for the presence of two or more autoimmune diseases in the same person [36]. Other explanations have been identified when anti-TNF-a treatment improved thyroid function in hypothyroid patients with RA [37]; provide a suggestion that inflammatory cytokines may play a pathogenic role in thyroid dysfunction[38].

This study showed positive correlations between serum levels of TSH and RA activity parameters (ESR, CDAI), and we found inverse correlations between serum levels of FT3, FT4 and RA activity index (CDAI), but in both conditions, the correlations did not reach the statistically significant value, P value > 0.05, as shown in (table 5). These results were inconsistent with study of *Elattar et al.*[14]that found significant positive correlations between serum levels of TSH and RA activity parameters (ESR, DAS28) which indicate that higher levels of TSH are associated with higher RA disease activity, and significant inverse correlations between serum levels of FT3 and RA activity parameters (ESR, DAS28), indicating that lower levels of FT3 are associated with higher RA disease activity. The study of *Joshi et al.* [39] also found significant correlations between serum levels of TSH and

disease activity parameters (ESR and DAS28). The difference in the results between our study and other studies may be due to small patients sample or may be due to different parameters used to measure disease activity as we used (CDAI) while *Alattar et al* study and *Joshi et al.* study had used DAS28.

In this study, the results indicate there was no significant association between the activity of disease and thyroid status. Although the thyroid dysfunction (mainly hypothyroidism) was reported higher with patients of moderate activity status (CDAI 11-21), the difference did not reach the significant level (p=0.5) as shown in (table 8). The study results are consistent with *Punzi L et al.*[34], and study of *Singh B et al.*[40], who found there is no significant association between hypothyroidism and RA disease activity state, and these studies suggested that the thyroid dysfunction may be related to disease duration rather than disease activity. current study was not consistent with the study of *Elattar et al.* [14] and *Joshi et al.* [39] that showed a significant correlation of hypothyroidism and the disease activity parameters; as we said this could be due to smaller sample group included in the current study, and different parameters used.

The results showed that the hypothyroid status was reported in 20 patients of RF-positive status in comparison to only one patient of RF-negative status, in addition, the incidence of subclinical hypothyroid and hyperthyroid status was higher with patients of RF positive status and this association was significant (P value=0.01). ACPA was not found to have a significant association with co-existing RA and thyroid dysfunction (P value= 0.2). These results in agreement with the study of *Mosli et al.* [41] that found there is a significant association between RF- positive RA and hypothyroidism, while ACPA was not found to have significant association. The study of *Shiroky et al.*[29] found there is no association between thyroid dysfunction and RF status, and the study of *joshi et al.* [39] found no association between thyroid dysfunction (mainly hypothyroidism) and RF status or ACPA status.

Conclusions

Thyroid dysfunction is more frequent in RA patients compared to healthy population and hypothyroidism is the most common type of thyroid dysfunction in RA patients. There are no significant associations between overall thyroid dysfunction or subclasses of thyroid dysfunction and RA disease activity.

Recommendations

1- Performance of thyroid function tests in patients with RA as a part of biochemical and immunological profiles and regular follow up for long period may help in early detection of associated thyroid dysfunction.
2- Thyroid abnormalities in RA patients should be taken in account by clinicians due to possible overlap between the symptoms of RA and thyroid diseases.
3- Further studies with larger sample size and longer duration are highly suggested, for further investigation such as ant-thyroid antibodies and for investigate the correlation between thyroid dysfunction and RA activity measured by other parameters.

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