Original Article

Impacts of Hashimoto's Thyroiditis on Rheumatoid Arthritis Activity and Its Complication Among Iraqi Patients with Rheumatoid Arthritis

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Abstract

Background: Rheumatoid arthritis (RA) is an autoimmune disorder. Autoimmune thyroid disease often coexists with RA and is associated with elevated cardiovascular (CV) risk. This risk was pronounced in women and the elderly. RA patients should be closely monitored to prevent the development of hypothyroidism. **Objectives:** The purpose of this study was to investigate the impacts of Hashimoto's thyroiditis on rheumatoid arthritis activity and its complication among Iraqi patients with rheumatoid arthritis. **Materials and Methods:** This study is a cross-sectional observational study involving 140 participants diagnosed with RA (according to rheumatologist physicians in accordance with ACR/EULAR 2010 criteria). Enzyme-linked immunosorbent assay (ELISA) was used to assess serum levels of anti-CCP, Ab-TPO, TSH, T4, and lipid profile. As well as troponin, myoglobin, and creatine kinase were measured. RA activity was estimated according to DAS-28-ESR and CDAI. Patients included 16 males and 124 females, ranging between the ages of 20 and 60 years. **Results:** The current study revealed a significant difference between anti-TPO levels in the serum of RA patients with DAS-28ESR (P = 0.006). Also, the study showed a strong positive correlation (r = 0.436) between anti-TPO and DAS-28-ESR. **Conclusion:** HT is frequent among patients with RA. Therefore, there is a need for screening of thyroid hormone dysfunction as well as the presence of anti-TPO in RA patients particularly in young patients, females, and those with high disease activity. No significant differences in the occurrence of CVD among RA patients with HT and euthyroid RA patients.

Keywords: Anti-TPO, autoimmune thyroid disease, CVD, Hashimoto's thyroiditis, rheumatoid arthritis, rheumatoid arthritis activity

Introduction

Rheumatoid arthritis (RA) is an inflammatory disease that affects the joints found in the limbs. It mostly presents as recurring, persistent inflammation in the joints. When the disease is advanced, the heart, skin, as well as other tissues and organs may have serious impediments as a result of joint abnormalities and impairments.[1]

The complicated, chronic, inflammatory, and autoimmune characteristics of RA likely contribute to the high prevalence of extra-articular manifestations (EMs) and comorbidities associated with the disease.[2] Dermatological, cardiovascular, pulmonary, gastrointestinal, ophthalmic, renal, and neurological manifestations are all examples of RA's extra-articular involvement.[3]

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Quick Response Code:

Website: https://journals.lww.com/mjby

DOI: 10.4103/MJBL.MJBL_1376_23

Autoimmune thyroid disease (AITD) is one of the most prevalent autoimmune comorbidities in RA patients.[4] RA and autoimmune thyroid disease are frequently found together and are both risk factors for cardiovascular disease.[5] While the exact mechanism through which RA and AITD are linked remains unknown, numerous studies have shown autoimmunity as a key player in the development of both conditions. Some genes, including STAT4, HLA-DRB1, and the vitamin D receptor, were

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Submission: 10-Sep-2023 **Accepted:** 06-Dec-2023 **Published:** 24-Sep-2024

How to cite this article: Diab BA, Obaid RF. Impacts of Hashimoto's thyroiditis on rheumatoid arthritis activity and its complication among Iraqi patients with rheumatoid arthritis. Med J Babylon 2024;21:646-52.

also found to have important roles in the progression of both disorders.[3]

The most common form of autoimmune thyroid disease (AITD) is Hashimoto's thyroiditis (HT). Antibodies against the thyroid-stimulating hormone receptor and the enzyme thyroid peroxidase (TPO) that catalyzes the synthesis of thyroid hormones are hallmarks of HT.[6]

Several studies have linked hypothyroidism to a worsening of rheumatoid arthritis, particularly the destructive arthropathy that mostly affects the proximal interphalangeal joints.[7]

In addition, current research has shown that the presence of AITD as a coexisting condition can increase the severity and activity of RA.[8]

Following the patient's RA diagnosis at the first appointment, the disease activity and treatment response were compared to those at the 3- and 6-month follow-up visits. RA patients with AITD scored worse on patient-reported measures of disease activity, such as pain and general health, but not on objective measures of disease activity recorded by the clinician. Patients with RA and AITD should be evaluated using both subjective and objective indicators of disease activity in clinical practice.[9]

Thyroiditis and thyroid dysfunction can be identified using anti-TPO. Eighty to ninety percent of patients with AIT have detectable levels of circulating anti-TPO. For the diagnosis of AITD, the detection of circulating anti-TPO has a sensitivity of 90%. Female patients with anti-TPO have a higher occurrence of postpartum thyroiditis. The role of anti-TPO in the immune-pathogenesis of hypothyroidism in AIT has been suggested by a number of studies. Both antibody-dependent cellular cytotoxicity by natural killer (NK) cells and complement-dependent cytotoxicity contribute to the death of thyrocytes and the development of thyroid atrophy when stimulated by anti-TPO.[10] anti-TPO Ab levels have also been shown to correlate with TNF and IFN production.[11]

The purpose of this study was to investigate the impacts of Hashimoto's thyroiditis on rheumatoid arthritis activity and its complication among Iraqi patients with rheumatoid arthritis

Materials and Methods

Patients

Participants in this research were Iraqi people (as patients) with RA who attended the Rheumatology department in Al-Sadr Medical City in Najaf. This research was carried out on a total of 140 participants diagnosed RA determined by rheumatologist doctors in line with ACR/EULAR 2010 Criteria and serological testing. Patients included 16 males and 124 females, ranging between the ages of 20 and 60. Each patient was questioned about their name, gender, age, and any other items. The duration of RA disease in patients included in this study was a maximum of 30 years and a minimum of months, with information coming from rheumatologist questionnaires filled up by patients with RA, by using the DAS-28-ESR and the CDAI for patients, the current study was able to categories RA patients into mild, moderate, and severe categories according to the DAS-28-ESR by the use of the equation on the website (https://www.4s-dawn.com/DAS28/).

Participants who have other rheumatologically diseases, prior thyroidectomy, pregnant women, evidence of malignancy, patients who have chronic liver or renal diseases, or hyperthyroidism will be excluded.

Sample collection

The sample collected of venous blood was from 5 to 10 mL. The blood sample was divided into 2 mL was placed in a disposable ESR tube for the Westergren method of measuring ESR, and 3–7 mL was placed in a sterile gel tube for further analysis. After the blood was drawn in its whole, it was left undisturbed at room temperature to clot. About 10-20 min is average for this. Centrifugation at 3000 rpm for 20 min was used to dislodge the clot. The sample needs to be centrifuged once more if precipitates form during the reservation. Each patient's sample was separated into three parts and stored in an Eppendorf tube at temperatures ranging from –20°C to –45°C. ELISA was employed for the measurement of ACCP, thyroid-stimulating hormones (TSH), thyroxin (T4), and anti-thyroperoxidase (anti-TPO). Lipid profile measurement by spectrophotometer. Also determination of heart enzymes (troponin, myoglobin, and creatine kinase) in RA patients by rapid test (Immuno-chromatography).

Statistical analysis

The SPSS program, version 26, was utilized to analyze the data. Descriptive statistics was done through the calculation of frequency, percentage, mean, and standard error of the mean of sociodemographic characteristics of the study sample presented by tables and bar charts. After testing the normality of data, inferential statistics were by the application of and independent *t* test and ANOVA to differentiate the means of rheumatoid and autoimmune thyroiditis markers in addition to testing the correlation and regression relationship of some numerical parameters. Chi square and Fisher's exact probability tests were applied for the categorical association. Statistical analysis was applied. Statistical significance was regarded as having a *P* value that must be equal to or less than 0.05.

Ethical approval

Prior to the start of the study, the ethical committee of the Faculty of Medicine, University of Kufa, provided

its permission. Individuals' informed agreement was also gained.

Results

Descriptive of study group

The study included 140 RA patients. The sociodemographic characteristics of the involved individuals in this study are presented in Table 1; The patients included 16 males (11.4%) and 124 (88.6%) females. According to the age, the majority of RA patients are among the age group older than 40 years (70%), the mean age of patients was (47.1 ± 13). The results show that the majority of cases were among married 133 (95%), among urban residents 111 (79.3%), and 129 (92.1%) among the unemployed.

Distribution of study sample with and without Hashimoto's disease by associated comorbidities

Table 2 shows no significant difference in *P* value (>0.05), in the occurrence of CVD, hypertension, and DM among euthyroid, subclinical, and overt HT groups.

The mean of study markers in relation to (DAS-28 ESR) of rheumatoid arthritis

Table 3 clarifies the comparison study parameters according to DAS-ESR. There were highly significant differences (*P* value = 0.0001) in the concentration of ESR according to DAS-ESR [Figure 1].

Association between Hashimoto's thyroiditis and heart enzyme among study group (RA patients)

Table 4 shows no significant difference in *P* value (>0.05), among euthyroid RA patients, subclinical HT, and overt HT patients according to the positivity and negativity of heart enzymes (troponin, myoglobin, creatine kinase).

Comparison of lipid profiles according to clinical status of Hashimoto's disease

Table 5 shows no significant difference in Lipid profile that includes (TG, HDL, TC, LDL, and VLDL) (*P* value > 0.05) among euthyroid, subclinical, and overt HT groups.

Table 1: Sociodemographic characteristics of the study samples with rheumatoid arthritis (*N* = 140)

Variables		Frequency	Percent
Age group (year)	≤40	42	30.0
	>40	98	70.0
	Total	140	100.0
Mean age ± SD		47.1 ± 13	
Gender	Female	124	88.6
	Male	16	11.4
	Total	140	100.0
Occupation	Unemployed	129	92.1
	Employed	8	5.7
	Students	3	2.1
	Total	140	100.0
Marital status	Married	133	95.0
	Single	7	5.0
	Total	140	100.0

Table 2: Distribution of study sample with and without Hashimoto's disease by associated comorbidities

Characteristics			Study sample (*N* = 140)			Total	*P* value
			Subclinical hypothyroidism (*N* = 9)	Overt hypothyroidism (*N* = 36)	Euthyroid (*N* = 95)		
CVD	No	Count (%)		34 (94.4)	92 (96.8)	135 (96.4)	0.673
	Yes	Count (%)	0 (0.0)	2 (5.6)	3 (3.2)	5 (3.6)	
Total		Count (%)	9 (100.0)	36 (100.0)	95 (100.0)	140 (100.0)	
Hypertension	Yes	Count (%)	2 (22.2)	8 (22.2)	21 (22.1)	31 (22.1)	1.000
	No	Count (%)	7 (77.8)	28 (77.8)	74 (77.9)	109 (77.9)	
Total		Count (%)	9 (100.0)	36 (100.0)	95 (100.0)	140 (100.0)	
DM	Yes	Count (%)	2 (22.2)	8 (22.2)	19 (20.0)	29 (20.7)	0.955
	No	Count (%)	7 (77.8)	28 (77.8)	76 (80.0)	111 (79.3)	
Total		Count (%)	9 (100.0)	36 (100.0)	95 (100.0)	140 (100.0)	

Table 3: Mean difference of study markers in relation to disease activity score (DAS-28 ESR) of rheumatoid arthritis

Markers by RA severity (DAS)		*N*	Mean	Std. error	95% confidence interval for mean		*P* value
					Lower bound	Upper bound	
ESR, mm/h	Severe	62	41.15	2.144	36.86	45.43	0.000
	Moderate	49	28.49	2.262	23.94	33.04	
	Mild	29	24.14	3.636	16.69	31.59	
	Total	140	33.19	1.563	30.10	36.28	
Anti-CCP, U/mL	Severe	62	69.74406	4.992025	59.76189	79.72623	0.000
	Moderate	49	47.40959	5.977072	35.39188	59.42730	
	Mild	29	18.35082	5.005727	8.09705	28.60458	
	Total	140	51.28125	3.598119	44.16713	58.39537	
Anti-TPO, IU/mL	Severe	62	66.35937	10.302201	45.75884	86.95989	0.006
	Moderate	49	37.90381	10.434018	16.92481	58.88281	
	Mild	29	15.32634	9.561451	−4.25941	34.91208	
	Total	140	45.82880	6.362990	33.24803	58.40956	
TSH, IU/mL	Severe	62	3.49428	0.308789	2.87682	4.11174	0.004
	Moderate	49	2.56295	0.293714	1.97240	3.15350	
	Mild	29	1.91810	0.304156	1.29507	2.54114	
	Total	140	2.84182	0.188790	2.46855	3.21509	
T4, ng/dL	Severe	62	0.98829	0.060421	0.86747	1.10911	0.001
	Moderate	49	1.25835	0.055449	1.14686	1.36984	
	Mild	29	1.25336	0.056291	1.13805	1.36867	
	Total	140	1.13772	0.036620	1.06531	1.21012	

Post hoc TESTS

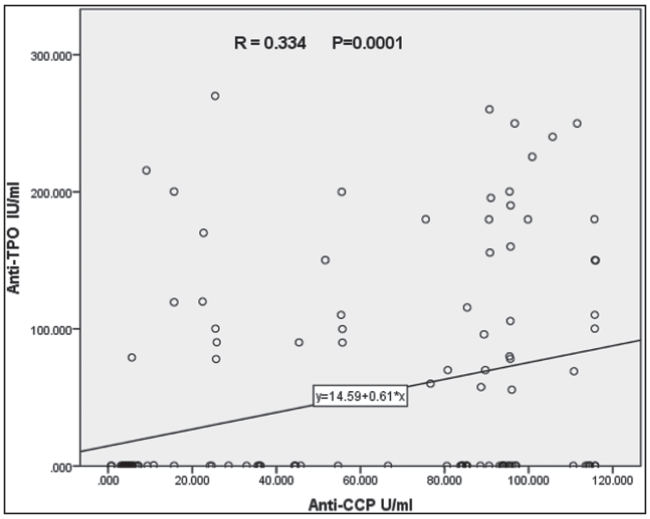

Figure 1: Correlation between serum anti-CCP and anti-TPO levels among patients with rheumatoid arthritis. There is a highly significant positive correlation in serum level of anti-CCP and anti-TPO serum estimate among the study sample of rheumatoid ($P = 0.0001$)

Discussion

Sociodemographic and clinical parameters of study

The findings of this study indicated that most RA patients are over 40 years old (70%). This result is agreeing to the study by Cope,[12] who found that the age at the beginning of RA is high among the age group of 45–75 years.

In terms of patient age, the current study indicated that patients with RA had an average age of 47.1 ± 13 years. This finding is consistent with the study by Raslan *et al.*,[13] who reported an average age of 46.2 ± 12.2 years.

According to the findings of this research, the majority of RA patients were females 124 (88.6%) as compared with males 16 (11.4%), which was agreed to a previous local study done in Iraq.[14]

In terms of marital status, the majority of the patients (95%) were married, which agrees with Karahan,[15] who found that the majority were married (91.9%).

Hypertension and diabetes mellitus accounted for 27.1% and 18.6% of the total, respectively. These results were comparable with a study conducted in the USA by Chen,[16] who found that 36.1% of RA patients had hypertension, and with Kochi,[17] who indicated that 22.1% had diabetes mellitus.

CVD accounted for 3.6% of the total, these results were comparable with a study conducted in Saudi Arabia by Alanazi,[18] who indicated that 1.7% of RA patients had CVD. Also, McCoy[19] discovered that 6.1% ± 1.2% of RA patients had a cumulative incidence of CVD.

The unemployed patients accounted for 92.1% of the total. This was comparable with a study conducted in South Africa by Mabusela,[20] who found that 87.3% of RA patients had been unemployed.

Only 20.7% out of 140 RA patients had a family history. This result was nearly similar to the study by

Table 4: Association between heart enzyme and Hashimoto's thyroiditis among study group

Markers			Associated Hashimoto's disease			Total	*P* value
			Subclinical	Clinical	Euthyroid		
Troponin	Negative	Count	8	34	94	136	0.188
		%	88.9	94.4	98.9	97.1	
	Positive	Count	1	2	1	4	
		%	11.1	5.6	1.1	2.9	
Total		Count	9	36	95	140	
		%	100.0	100.0	100.0	100.0	
Myoglobin	Negative	Count	9	33	91	133	0.487
		%	100.0	91.7	95.8	95.0	
	Positive	Count	0	3	4	7	
		%	0.0	8.3	4.2	5.0	
Total		Count	9	36	95	140	
		%	100.0	100.0	100.0	100.0	
Creatine Kinase	Negative	Count	8	34	93	135	0.288
		%	88.9	94.4	97.9	96.4	
	Positive	Count	1	2	2	5	
		%	11.1	5.6	2.1	3.6	
Total		Count	9	36	95	140	
		%	100.0	100.0	100.0	100.0	

Table 5: Comparison of lipid profiles according to clinical status of Hashimoto's disease

Laboratory estimates (mean ± SE)	Study sample (*N* = 140) (mean ± standard error)			*P* value
	Subclinical HT (*N* = 9)	Overt HT (*N* = 36)	Euthyroid (*N* = 95)	
TG, mg/dL	137.93 ± 4.96	156.81 ± 5.05	172.20 ± 9.04	0.294
HDL, mg/dL	31.78 ± 1.63	35.83 ± 1.05	33.68 ± 586	0.082
TC, mg/dL	178.63 ± 9.95	193.22 ± 7.79	178.61 ± 3.93	0.175
LDL, mg/dL	166.66 ± 7.34	178.20 ± 7.196	179.36 ± 5.49	0.765
VLDL, mg/dL	27.59 ± 99	31.36 ± 1.01	34.44 ± 1.81	0.294

Shrivastava,[21] who indicated in their study the percentage of the patient with RA was 14%. Frisell[22] revealed in their study a family history of rheumatoid arthritis did not affect how RA manifested clinically. In contrast, Gossec[23] demonstrates that seropositive RA has a heredity estimate of 40%–65%, whereas seronegative RA has a heritability estimate of 20%.

In a recent study, we find a significant difference in anti-TPO, TSH, and T4 according to the severity of RA (DAS-28-ESR and CDAI) (P value < 0.05). Abnormality in these markers was higher in severe DAS-ESR and CDAI than in moderate and mild cases. There was a highly positive correlation between anti-TPO and DAS-ESR (r = 0.436), and also a highly positive correlation between TSH and DAS-ESR (r = 0.401). T4 shows an inverse correlation with CDAI and a strong inverse correlation with DAS-28-ESR.

This agrees Emamifar[24] that find higher RA disease severity was found to be substantially correlated with elevated serum TSH, and anti-TPO levels. Also, Elattar[25] found a positive correlation between TSH and measures of RA disease activity. Koszarny[26] found that anti-thyroid antibodies, particularly anti-TPO levels, are positively correlated with DAS-28-ESR.

Correlation of autoimmune hypothyroidism with CVD

Individuals diagnosed with RA and hypothyroidism, both in clinical or subclinical forms, exhibit a heightened susceptibility to cardiovascular disease (CVD). This elevated risk can potentially be attributed to the presence of endothelial dysfunction resulting from inflammation, which subsequently leads to a reduction in nitric oxide levels.

In a recent study, there are no significant differences in the occurrence of CVD among RA patients with HT (clinical and subclinical) and RA patients without HT (P value = 0.673). This outcome was comparable with Hueston,[27] who found there is no association of subclinical hypothyroidism with an increased risk of heart inflammation.

McCoy[19] found that Subclinical hypothyroidism in RA patients was not associated with cardiovascular disease

or death, however, Hashimoto's disease was strongly connected with cardiovascular disease in RA patients. Our results disagree with Huang[28] and Agca[5] that who find the presence of subclinical hypothyroidism in RA patients is associated with a higher likelihood of experiencing new cardiovascular (CV) events when compared to RA patients who have normal thyroid function. In a recent study, there are no significant differences in the abnormality of lipid profile (TG, HDL, TC, LDL, VLDL) among RA patients with HT (clinical and subclinical) and euthyroid RA patients, *P* value = (0.294, 0.082, 0.175, 0.765, and 0.294) respectively. This agrees with Raterman,[29] which discovered no significant difference in lipid profile among RA patients and hypothyroid patients ($P > 0.05$). And disagree with Roldan,[30] that found significant differences in hypercholesterolemia among RA patients with HT (clinical and subclinical) and RA patients without HT, $P = 0.045$.

There are no significant differences in the positivity or negativity of heart enzymes (Troponin, myoglobin, and creatine kinase) among RA patients with HT (clinical and subclinical) and RA patients without HT, *P* value = (0.188, 0.487, and 0.288) respectively.

Conclusions

The association was significant among RA patients with HT and DAS-28-ESR, CDAI, ACCP, BMI, and ESR. No significant differences in the occurrence of CVD among RA patients with HT and euthyroid RA patients. TSH and anti-TPO of RA patients with HT are significantly higher as compared to euthyroid RA patients. There was a positive correlation between anti-TPO and TSH with ESR and a strong positive correlation with DAS-28-ESR, CDAI, and anti-CCP. There were no significant differences in the abnormality of lipid profile (TG, HDL, TC, LDL, VLDL) among RA patients with HT and euthyroid RA patients. There were no significant differences in the positivity or negativity of heart enzymes (troponin, myoglobin, and creatine kinase) among RA patients with HT and euthyroid RA patients.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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