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The prevalence of thyroid dysfunction and thyroid autoantibodies among patients with rheumatoid arthritis

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Abstract

Background and objective: Rheumatoid arthritis is a chronic and inflammatory autoimmune systemic disease of unknown cause that may affect many tissues and organs. Rheumatoid arthritis and thyroid disorders may occur in the patient simultaneously. The main antigens that give rise to thyroid antibodies are thyroglobulin, thyroid peroxidase, anti-cyclic citrullinated protein, and thyroid hormone receptor. This study aimed to determine the frequency of thyroid dysfunction and seroprevalence of anti-thyroid antibody in patients with rheumatoid arthritis and its association with inflammatory marker C-reactive protein.

Methods: A cross-sectional study was performed at Rizgari Teaching Hospital and CMC private hospital, Erbil, Iraq. From 15 January to15 October 2020. A hundred patients with rheumatoid arthritis were included in the study, in addition to 70 controls. The serum levels of biomarkers were determined by the chemiluminescent immunoassay method.

Results: Patients with rheumatoid arthritis had 6% of thyroid dysfunctions. Regarding the prevalence of thyroid autoantibodies in patients with rheumatoid arthritis, 9% had positive anti-thyroid peroxidase, 13% had positive anti-thyroglobulin, and 6% were positive for a combination of both. There was a statistically significant (P <0.001) high level of serum anti-cyclic citrullinated protein and C-reactive protein in rheumatoid arthritis than in control. Euthyroid profiles were 73% inrheumatoid arthritis patients and 82.9% in control.

Conclusion: The study delineated the co-existence of thyroid disorder in rheumatoid arthritis patients with or without autoimmune origin, besides the increased prevalence of auto-thyroid antibody among rheumatoid arthritis with thyroid dysfunction.

Keywords: Rheumatoid arthritis; Thyroid dysfunction; Anti-thyroid peroxidase; Anti-cyclic citrullinated protein.

Introduction

Rheumatoid arthritis is a chronic and systemic autoimmune disease that can result in continual inflammatory polyarthritis and continuous joint devastation. Rheumatoid arthritis is characterized by immune cell infiltration in the small joints of the hands and feet in a symmetric distribution, doing to damaged mobility and increased disability.[1-2] The prevalence of rheumatoid arthritis in the general population is ~0.5-1%.[2]

The autoimmune diseases tend to affect females more than males with varying frequency conformity to disease and organ/body system.[2] Smoking is the main environmental risk. Genetic and environmental factors contribute to the development of rheumatoid arthritis.[3] The disorder is most typical in elderly people, and rheumatoid arthritis prevalence increases after the age of 25 years, with greater involvement of populations between 35 and 55 years.[4]

Rheumatoid arthritis is related to some comorbidities, also directly correlated with the risk of other chronic diseases involving cardiovascular diseases, making it one of the major public health problems.[5] Biomarkers such as rheumatoid factor and

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anti-citrulline peptide (ACCPA) have been shown to precede a clinical diagnosis of rheumatoid arthritis. With ACCPA being strongly predictive of the future development of rheumatoid arthritis.[6]

C-reactive protein (CRP), as a specific marker of systemic inflammation, is increased in patients with rheumatoid arthritis.[7] A relationship between rheumatoid arthritis and thyroid dysfunction with or without autoimmune origin has been reported in 6% to 34% of patients with rheumatoid arthritis.

Autoimmune thyroid disease covers a group of pathologies that involve thyroid dysfunction and the autoimmune response of this Hashimoto thyroiditis, characterized by hypothyroidism, and Graves' disease, characterized by hyperthyroidism.[9]

Autoimmune thyroid disease arises from an autoimmune response against gland antigens: Thyroid peroxidase (TPO), thyroglobulin (Tg), and thyroid hormone receptor (TSH-R). Two-thirds of Hashimoto thyroiditis patients and one-third of those with Graves' disease carry circulating Tg antibodies. The TPO antibody has a 90% prevalence in patients with Hashimoto thyroiditis, 75% of those with Graves' disease.[10] Being there the hallmark of Graves' disease, the existence of agonistic anti-TSH-R antibodies concerns nearly all cases of this pathology.[11]

Variables in the genes (e.g., PTPN22, CTLA4, and HLA-DR) involved in T-cell response regulation were associated with both rheumatoid arthritis and autoimmune thyroid disease, suggesting that co-genetics may be one factor linking the two conditions together. Whether there are other links between the two conditions, such as the causal effect of autoimmune thyroid disease on the onset of rheumatoid arthritis, shared environmental stimuli, and/or disease-modifying antirheumatic drugs that have a protective effect on autoimmune thyroid disease development, remains unclear.[12]

This overlap may explain the co-existence of different autoimmune diseases. This study aimed to find out the frequency of thyroid dysfunction and seroprevalence of anti-thyroid antibody in patients with rheumatoid arthritis and their association with inflammatory marker CRP.

Methods

A cross-sectional study with a comparison group was performed at the College of Medicine, Hawler Medical University, in cooperation with Rizgari Teaching Hospital and CMC private hospital, Erbil, Iraq. Patients with rheumatoid arthritis presenting to the Rheumatology Outpatient Department at Rizgari Teaching Hospital and CMC Private Hospital from January to October 2020 were included in the study. The study sample included 100 patients with rheumatoid arthritis in addition to 70 controls. Information on the whole individuals was recorded, including their gender and age group. Anthropometric measurements, including the height (m), weight (kg), and the calculated body mass index (BMI) kg/m2 were determined and Smoking.

A venous blood sample was drawn from each patient and placed in a yellow tube to separate the serum by centrifugation at 1500 rpm for 15 minutes. The separated serum was divided and added into three (0.5ml) of sterile Eppendorf tubes. All serum samples were frozen at -70 C to determine the inflammatory markers. Qualitative determination of CRP and a serum levels of anti-CCP, thyroid function antibodies including; free triiodothyronine fT3, free thyroxin fT4, thyroid stimulating hormone (TSH), anti-TGA and anti–TPO all were determined by using chemiluminescent immunoassay method (Cobas e411Roche Diagnostics, Indianapolis, IN, USA). According to the instruction of the manufacturers.

Thyroid disturbances were further classified into Euthyroid: if FT4, FT3 and TSH were normal; Hypothyroidism: when the TSH was raised together with a decreased FT4; Hyperthyroidism: that

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TSH was low with normal or high FT4; Subclinical hypothyroidism if the TSH was high level with normal FT4; Subclinical hyperthyroidism: that TSH was low with normal FT4; Euthyroid sick syndrome: TSH that normal with low FT3 and normal or low FT4.

Inclusion criteria

This study included rheumatoid arthritis patients who fulfilled the European Association Against Rheumatology (EULAR) / American College of Rheumatology (ACR) - 2010 criteria for rheumatoid arthritis and were screened for anti-CCP, CRP, Ft3, Ft3, TSH, anti-TPO, and anti-TG.

Exclusion criteria

The exclusion criteria included patients with a history of thyroidectomy, patients with malignancy on radiotherapy, women on oral contraceptives, patients on drugs causing hypothyroidism, pregnancy, sepsis, and serious underlying diseases including metabolic syndrome.

Statistical analysis and data management

The statistical package for the social sciences (SPSS, version 25) was used for data entry and analysis. The Chi-square test was used to show the significance of association, but when the expected values of more than 20% of the cells of the tables were less than five, Fisher's exact test was used. Comparing the means of two samples was done using the t-test of two independent samples. The strength of correlation between numerical variables was assessed by calculating the Pearson correlation coefficient. The level of significance was less than 0.05.

Ethical consideration

The study was approved by the Research Ethical Committee of the College of Medicine, Hawler Medical University, Erbil.

Results

Table 1 shows laboratory characteristics of rheumatoid arthritis patients as compared with controls. A hundred patients with rheumatoid arthritis were included in this study, in addition to 70 controls. The mean age ± SD of the rheumatoid arthritis patients was 50.71 ±12.01 years, and that of the controls was 47.27 ± 17.83 years (P = 0.163). As far as age, rheumatoid arthritis was most prevalent among patients with age 40-49 (36%), followed by the age group 50-59 (31%).

Regarding control, the matched age group were selected similar to that rheumatoid arthritis group. The majority (87.6%) of the whole sample were females, but there was no significant difference between the patients and the controls regarding the gender distribution (P = 0.759). One fifth (20%) of the rheumatoid arthritis patients were smokers compared with 11.4% of the control group (P = 0.138). Regarding body mass index (BMI), 35% of the rheumatoid arthritis patients were overweight and 40% were obese, with no significant differences in the BMI with that of the control group, as presented in Table 1.

It is evident in Table 2 that 73% of the rheumatoid arthritis patients had normal thyroid function compared with 82.9% of the controls, but the difference was not significant (P = 0.334). More details of the thyroid function of the two groups are presented in Table 2.

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Table 1 Basic characteristics of the studied sample

Characteristic	Rheumatoid		Control		Total		*P* value
	No.	(%)	No.	(%)	No.	(%)	
Age (years)							
< 30	4	(4.0)	14	(20.0)	18	(10.6)	
30-39	8	(8.0)	13	(18.6)	21	(12.4)	
40-49	36	(36.0)	10	(14.3)	46	(27.1)	
50-59	31	(31.0)	13	(18.6)	44	(25.9)	
60-69	13	(13.0)	8	(11.4)	21	(12.4)	
70-79	8	(8.0)	12	(17.1)	20	(11.8)	<0.001
Mean (±SD)	50.71	(±12.01)	47.27	(±17.83)			0.163†
Gender							
Male	13	(13.0)	8	(11.4)	21	(12.4)	
Female	87	(87.0)	62	(88.6)	149	(87.6)	0.759
Smoking							
Yes	20	(20.0)	8	(11.4)	28	(16.5)	
No	80	(80.0)	62	(88.6)	142	(83.5)	0.138
BMI							
< 25	25	(25.0)	19	(27.1)	44	(25.9)	
25-29	35	(35.0)	24	(34.3)	59	(34.7)	
≥ 30	40	(40.0)	27	(38.6)	67	(39.4)	0.951
Total	**100**	**(100.0)**	**70**	**(100.0)**	**170**	**(100.0)**	

Table 2 Classification of thyroid function of the two study groups

Thyroid dysfunction	Rheumatoid		Control		Total		*P* value
	No.	(%)	No.	(%)	No.	(%)	
Hypothyroidism	1	(1.0)	1	(1.4)	2	(1.2)	
Subclinical hypothyroidism	4	(4.0)	1	(1.4)	5	(2.9)	
Subclinical hyperthyroidism	1	(1.0)	2	(2.9)	3	(1.8)	
Normal (euthyroid)	73	(73.0)	58	(82.9)	131	(77.1)	
Euthyroid sick syndrome	20	(20.0)	7	(10.0)	27	(15.9)	
Unclassified (High T3)	1	(1.0)	1	(1.4)	2	(1.2)	0.334*
Total	100	(100.0)	70	(100.0)	170	(100.0)	

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Figure 1 shows that 92.4% of the rheumatoid arthritis were euthyroid, compared with 93.5% of the control group (P = 0.684).

As illustrated in Table 2 and Figure 1, the frequency of thyroid dysfunction was as follows; 4% with subclinical hypothyroidism, 1% with hypothyroidism, and 1% with subclinical hyperthyroidism. When compared to that of the control group, subclinical hyperthyroidism was reported in 2.9%. The frequency of subclinical hypothyroidism was 1.4% and the same result was for hypothyroidism (1.4%).

Table 3 shows that 8.2% of the whole sample had positive anti TPO (9% in rheumatoid arthritis patients and 7.1% in control), 10.6% had positive Anti Tg (13% in rheumatoid arthritis patients and 7.1% in control), and 4.7% (6% in rheumatoid arthritis patients and 2.9% in control) were positive for the combination of both. No significant differences were detected between the two groups regarding the mentioned tests (P = 0.665, P = 0.222, and P = 0.473, respectively).

Table 3 Anti TPO and Anti Tg results of the two study groups

	Rheumatoid arthritis		Control		Total		*P* value
	No.	(%)	No.	(%)	No.	(%)	
Anti TPO							
Positive	9	(9.0)	5	(7.1)	14	(8.2)	
Negative	91	(91.0)	65	(92.9)	156	(91.8)	0.665
Anti Tg							
Positive	13	(13.0)	5	(7.1)	18	(10.6)	
Negative	87	(87.0)	65	(92.9)	152	(89.4)	0.222
Anti TPO & anti Tg							
Positive	6	(6.0)	2	(2.9)	8	(4.7)	
Negative	94	(94.0)	68	(97.1)	162	(95.3)	0.473*
Total	100	(100.0)	70	(100.0)	170	(100.0)	

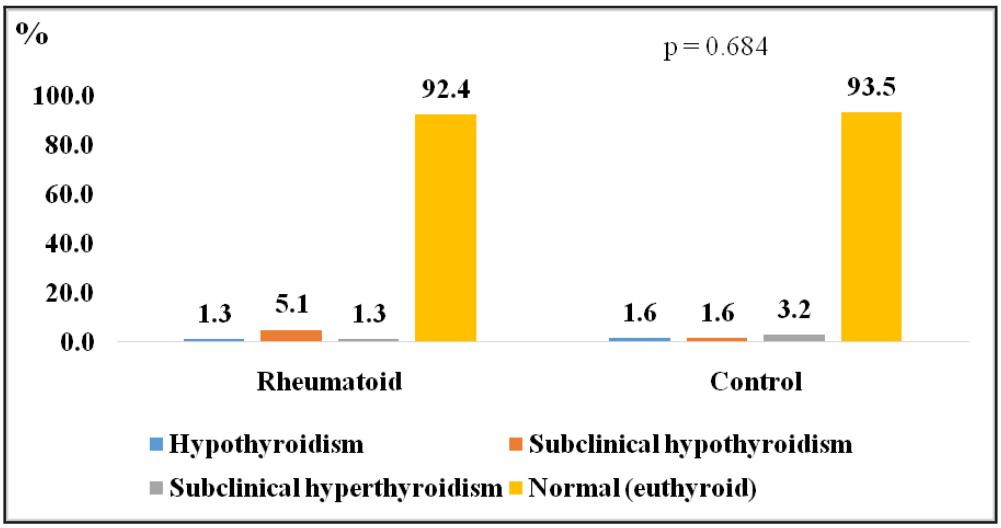

Figure 1 Normal and abnormal thyroid function among the two study groups

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It is evident in Table 4 that 6% of the rheumatoid arthritis group had low T3 levels compared with 2.9% of the control group, and 1% of the rheumatoid arthritis group had high T3 compared with 1.4% of the control group (*P* = 0.743). The rate of low T4 was 15% in the rheumatoid arthritis group, compared with 11.4% in the control group. Only one patient in the rheumatoid arthritis group had high T4, while none of the controls had high T4 (*P* = 0.794). No significant differences were detected between the two groups in the TSH levels (*P* = 0.584). Regarding the means of the mentioned variables, all the differences were not significant between the study groups.

The mean of anti CCP of the rheumatoid arthritis group (111.8 U/ml) was significantly (*P* <0.001) higher than the mean of the control (6.0 U/ml). The mean of CRP of the rheumatoid arthritis group (12.86 mg/L) was significantly (*P* <0.001) higher than the mean of the control (4.72 mg/L) as presented in Table 5.

The table shows no significant differences between the study groups regarding the means of anti Tg (*P* =0.747) and anti TPO (*P* = 0.508), as shown in Table 5.

Table 4 Thyroid hormones among rheumatoid patients and the controls

Hormone	Rheumatoid		Control		Total		*P* value
	No.	(%)	No.	(%)	No.	(%)	
Free T3 (pmol/L)							
Low	6	(6.0)	2	(2.9)	8	(4.7)	
Normal	93	(93.0)	67	(95.7)	160	(94.1)	
High	1	(1.0)	1	(1.4)	2	(1.2)	0.743*
Mean (±SD)	4.27	(±0.81)	4.36	(±0.87)			0.497†
Free T4(pmol/L)							
Low	15	(15.0)	8	(11.4)	23	(13.5)	
Normal	84	(84.0)	62	(88.6)	146	(85.9)	
High	1	(1.0)	0	(0.0)	1	(0.6)	0.794*
Mean (±SD)	15.04	(±2.94)	14.77	(±2.33)			0.536†
TSH (IU/mL)							
Low	1	(1.0)	2	(2.9)	3	(1.8)	
Normal	94	(94.0)	66	(94.3)	160	(94.1)	
High	5	(5.0)	2	(2.9)	7	(4.1)	0.584*
Mean (±SD)	1.91	(±2.01)	1.58	(±1.13)			0.222†
Total	**100**	**(100.0)**	**70**	**(100.0)**	**170**	**(100.0)**	

Table 5 Means of the numerical variables of the study groups

	Rheumatoid		Control		*P* value
	Mean	(±SD)	Mean	(±SD)	
Anti CCP (U/mL)	111.81	(±180.18)	6.00	(±0.00)	< 0.001
Anti Tg (IU/mL)	138.89	(±578.43)	111.12	(±511.46)	0.747
Anti TPO(IU/ml)	23.70	(±78.08)	16.47	(±56.10)	0.508
CRP (mg/L)	12.86	(±19.69)	4.72	(±5.97)	< 0.001

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In Table 6, six patients with rheumatoid arthritis and thyroid dysfunction were compared with 94 patients with rheumatoid arthritis but without thyroid dysfunction.

The mean age of those with thyroid dysfunction (60.67 years) was significantly (*P* = 0.036) higher than the mean age of those without thyroid dysfunction (50.07 years). The mean TSH of those with thyroid dysfunction was significantly higher than the mean of those without thyroid dysfunction (7.68 vs. 1.54 IU/mL). No significant differences were detected between the means of the following variables of those with and without thyroid dysfunction: free T3 (*P* = 0.767), free T4 (*P* = 0.804), anti CCP (*P* = 0.541), anti-TPO (*P* = 0.508) and anti Tg (*P* = 0.837).

Discussion

A clustering of specific autoimmune diseases such as thyroiditis and systemic autoimmune diseases such as rheumatoid arthritis diseases is usually co-existed in the patient at the same time. However, the reasons for these associations are not entirely evident.[13] The global prevalence of autoimmune thyroid disease in rheumatoid arthritis varies widely, ranging from 0.5% in Morocco to 27% in Slovakia and 38.3% in Egypt. The rate of the relationship between rheumatoid arthritis and thyroid dysfunction with or without autoimmune origin has been reported 6-34% in rheumatoid arthritispatients.[14] This high variability in prevalence might be attributed to difficulties in diagnosing autoimmune thyroid disease because it is based on the fact that there must be a prior diagnosis of a thyroid disorder. However, there has been much controversy over how to detect hypothyroidism or hyperthyroidism. The normal range of reference is not universally accepted, and therefore authors and clinicians worldwide accept different natural ranges.[15]

This study was carried out to determine and estimate the prevalence of thyroid dysfunction and thyroid autoantibody among patients of rheumatoid arthritis with or without clinical thyroid disorders and their relationship with disease activity and impairment of functioning. Rheumatoid arthritis can appear at any age but typically begins between the ages 25 and 70, which was consistent with the findings of our study. There was no statically significant difference in mean age between patients with rheumatoid arthritis (50.71) and healthy comparison (47.27).

Table 6 Means of the studied numerical variables by thyroid function among patients with rheumatoid arthritis

Variable	With thyroid dysfunction (n=6)		Without thyroid dysfunction (n=94)		*P* value
	Mean	(±SD)	Mean	(±SD)	
Age (years)	60.67	(±7.34)	50.07	(±11.99)	0.036
Free T3 (pmol/L)	4.36	(±1.08)	4.26	(±0.80)	0.767
Free T4(pmol/L)	14.75	(±3.78)	15.05	(±2.90)	0.804
TSH (IU/mL)	7.68	(±4.90)	1.54	(±0.84)	0.028
Anti CCP (U/mL)	67.95	(±151.75)	114.61	(±182.18)	0.541
Anti Tg (IU/mL)	91.44	(±133.61)	141.91	(±595.86)	0.837
Anti TPO (IU/mL)	44.29	(±66.29)	22.38	(±78.90)	0.508
CRP (mg/L)	10.91	(±10.37)	12.98	(±20.17)	0.804

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Only there was a statistical difference (*P* <0.01) at ages 70-79 years. An association between age and rheumatoid arthritis development is indistinct, but existing research mentions immunosenescence that occurs with aging can lead to chronic inflammation and immune-intermediated tissue damage.[12] Our study matches that of Hussein et al. and Ghitany et al.[6,17] The current study showed that the female gender was more frequent in rheumatoid arthritis patients, that 87% of rheumatoid arthritis patients were females versus 88.6% in the control group. There was no significant difference between the patients and the controls regarding the gender distribution. Female sex is associated with an increased risk of rheumatoid arthritis three times higher than men. Our result was consistent with other studies that showed female predominance in the context of rheumatoid arthritis, such as those performances by Elattar et al. and Mahagana et al.[18,19]

One fifth (20%) of the rheumatoid arthritis patients were smokers compared with 11.4% of the control group (*P* = 0.138), but there were no significant differences. Smoking leads to the rising expression of the enzyme PAD2, which increases the level of citrulline in the lung. Citrullination is the process of conversion of arginine into citrulline by an enzymatic reaction with peptidyl arginine deiminase (PAD), this matches with Källberg et al. and Anderson R et al.[3,20]

The largest proportion of the whole sample (39.4%) was obese, but there are no significant differences in the BMI distribution of the cases and controls. Obesity has been considered a risk factor for the development of rheumatoid arthritis that agree with Jian Feng et al. and England BR et al.[21-22]

A high significant statistical difference was observed among the studied groups regarding anti-CCP and CRP. The mean of anti CCP of the rheumatoid arthritis group (111.8 U/ml) was significantly (*P* <0.001) higher than the mean of the control (6.0 U/ml). Anti-CCP is more specific to detect rheumatoid arthritis specificity of ACPA IgG ~95% compared to controls. The presence of autoantibodies is considered predictive of the development of rheumatoid arthritis in patients with undifferentiated arthritis and the emergence of a more severe disease outcome with more erosions in the joints over time. This study agrees with the study done by Binesh et al. and Ghitany et al., which compared the diagnostic value of anti-CCP in patients with rheumatoid arthritis and controls that anti-CCP alone gives the best results in the diagnosis of rheumatoid arthritis.[6,23] The mean of CRP of the rheumatoid arthritis group (12.86 mg/L) was high significantly (*P* <0.001) higher than the mean of the control (4.72 mg/L). CRP is routinely evaluated as a traditional biomarker of systemic inflammation to help diagnose rheumatoid arthritis CRP increase in serum with unfavorable outcomes, including persistent disease, joint damage, and functional impairment. Our result agrees with Binesh et al.[23]

Regarding thyroid function tests, 73% of the rheumatoid arthritis patients had normal thyroid function compared with 82.9% of the control. However, no significant statistical difference was observed among the studied groups as regards serum, fT3, fT4, and TSH; this agrees with Ghitany et al.[6] According to thyroid function results, the thyroid dysfunction among the two groups was classified as hypothyroidism (1.2%) (subclinical hypothyroidism (2.9%), subclinical hyperthyroidism (1.8%) and euthyroid sick syndrome (15.9%). Our study confirmed an incidence of thyroid dysfunction in patients with rheumatoid arthritis compared with controls. This is consistent with many studies, such as the one by Li Q et al.[24] However, the results of this study were inconsistent with the study of Kumar et al.,[25] who found no statistically significant difference observed in the prevalence of thyroid disorders between

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the two groups. As thyroid autoimmune disease (TA-bs) simply can be differentiated from other thyroid dysfunctions by two prime tests, which rely on anti-thyroid peroxidase (anti-TPO) and tests anti-thyroglobulin (anti-Tg).

Our results regarding anti-TPO and anti-Tg were agreed with a study done by Saqre et al.,[14] who found that anti-Tg was positive in 26.7% and (anti-TPO) was positive in 33.3% of rheumatoid arthritis patients. Anti-Tg was positive in 3.3%, and (anti-TPO) was positive in 6.7% of controls. This tendency of increased prevalence of anti-TPO is consistent with previous studies.[26] Our results agree with Hussein et al.[17] The mean age of those with thyroid dysfunction (60.67 years) was significantly (P = 0.036) higher than the mean age of those without thyroid dysfunction (50.07 years). The mean of TSH in those with thyroid dysfunction was significantly (P = 0.028) higher than the mean of those without thyroid dysfunction (7.68 vs. 1.54 IU/mL). No significant differences were detected between the means of the other variables. Our results disagree with other studies by Lazurova et al. and Li et al., where the frequency of thyroid dysfunction among rheumatoid arthritis patients ranged between (27-32.2%) which was higher than that reported in this study (6%).[24,28] In addition, patients with thyroid dysfunction and rheumatoid arthritis are more prone to develop cardiovascular diseases.[27]

The prevalence of thyroid disorder in patients with rheumatoid arthritis patients leads to an increase in the severity of the disease and its exacerbation and more aggressive disease in rheumatoid arthritis patients.

Conclusion

The study delineated the co-existence of thyroid disorder in rheumatoid arthritis patients with or without autoimmune origin, besides increased prevalence of auto-thyroid antibody among rheumatoid arthritis with thyroid dysfunction.

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Competing interests

The authors declare that they have no competing interests.

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