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Original Research Article

ASSOCIATION OF THYROID DYSFUNCTION WITH AUTOIMMUNE THYROID DISEASE IN RHEUMATOID ARTHRITIS PATIENTS IN EASTERN INDIA

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ABSTRACT

Background: Rheumatoid arthritis (RA) is the chronic non-organ-specific autoimmune diseases. But, autoimmune thyroid disease (AITD) is the organ-specific autoimmune disease that can lead to hypo or hyper function of thyroid gland. Although the aetiology of both diseases is complex with a combination of genetic and environmental factors, there are overlaps in genes contributing to the pathogenesis of both diseases. Numerous studies found a correlation between thyroid abnormality and RA in different populations, yet some didn't. The present study is performed to evaluate the association of thyroid dysfunction with autoimmune thyroid disease in rheumatoid arthritis patients in Eastern Indian patients with RA.

Materials and Methods: A total of 671 RA patients and 592 healthy participants were included in this study. All participants underwent complete clinical and laboratory assessments. Participants were also assessed for thyroid function testing, including anti-TPO antibodies

Results: A significant association was found between RA disease and thyroid dysfunction which thyroid dysfunction was twice as common in RA patients as in controls (OR = 2.07, 95% CI: 1.42– 3.20; p-value > 0.001). Hypothyroidism was the most common thyroid dysfunction among RA patients (58 out of 84). Anti-TPO was significantly higher in 39 (36.44%) controls, and 143 (57.46%) cases and it was significantly more common in RA patients (OR = 2.69, 95% CI: 1.70–4.13; p-value 0.008).

Conclusion: RA disease was associated thyroid dysfunction especially AITD among the Eastern Indian population like several other populations.

Keywords: Rheumatoid arthritis, Thyroid dysfunction, Anti-TPO antibody, Autoimmune thyroid disease.

INTRODUCTION

Rheumatoid arthritis (RA) is one of the most prevalent autoimmune disorders affecting 0.46% of individuals all over the world and 0.7% of Indian population. RA is a multi-factorial disease which has both genetic and environmental causal factors in disease's pathogenesis.[1] RA disease can affect different aspects of lifestyle and physical activity that leads to disability.[2,3] Although RA mainly damages joints, it is a systemic disease, and approximately 40.6% of the patients have extra-articular manifestations.[4] Extra-articular involvement of RA consists of cutaneous, cardiovascular, pulmonary, gastrointestinal, ocular, renal, and neurologic presentations.[5]

Thyroid dysfunction is mainly divided into hypothyroidism and hyperthyroidism. Each of these can be further subdivided as overt and subclinical thyroid dysfunction.[6] Autoimmune thyroid disease (AITD) is the most prevalent organ-specific autoimmune disorder with a frequency of 5% within the public in general.[7] AITD is closely linked to, rheumatologic disease, including Sjögren syndrome, Systemic Lupus Erythematosus, and Systemic

sclerosis. RA and AITD connection were not fully investigated.[8,9]

Several studies determined various ranges of frequency of thyroid dysfunction, AITD, and anti-thyroid autoantibody like anti-thyroid peroxidase (anti-TPO) in RA patients in different places.[10] Although the mechanism of RA and AITD association is not fully understood yet, several studies showed autoimmunity as a vital factor in the pathogenesis of both diseases.[7] Some genes were also discovered to be key factors in both diseases' development such as STAT4, HLA- DRB1, and vitamin D receptor.[11] Due to the similar pathogenesis, there is a preponderance of such RA patients to be affected by autoimmune thyroid disease (AITD) and insufficient research have been done on this matter this study aimed to determine the association between RA and thyroid dysfunction, AITD, as well as anti-TPO positivity.

MATERIALS AND METHODS

Study Area: This hospital based cross-sectional study was conducted in the Department of Rheumatology with the collaboration of Department of Biochemistry of Medical College, Kolkata, West Bengal, India.

Ethics Statement: The study was approved and permitted by the institutional ethics committee for care and use of laboratory and started after obtaining the written consent from the concerned ethics committee.

Study Population: The present study was conducted between March 2022 and January 2025. Sample size was calculated at 95% confidence interval, with a power of 80% [12] using the formula

n = 4pq/d2

[p = Prevalence of RA (approximately 1% as per previous studies)

q = 100-p

d = allowable error (taken as 5%)]

= 670.6

This study included 671 patients with RA disease who presented to the outpatient clinic of Department of Pulmonary Medicine were selected by systemic random sampling method. All patients were aged between 18 and 65 on the basis of American College of Rheumatology and the European League against Rheumatism (ACR/EULAR) 2010 criteria for rheumatoid arthritis.[13]

Then 592 healthy persons with ESR and CRP within normal range along with RF negative of the same ages and sexes were included in this study as a control group from same region. Both the cases and controls were selected by a systemic random method.

Patients with chronic liver or renal disease, diabetes mellitus, concomitant infection, malignancy, any collagen vascular disease other than RA, pregnant females or patients consuming medication that can lead to thyroid dysfunction (e.g., interferon-α, dopamine agonists, amiodarone, anticonvulsant drugs, somatostatin analogs, and lithium) were excluded.

Clinical assessments: The data was collected by reviewing medical records of patients, interviews, and physical examination. Participants' demographic features were also taken into consideration. They were also evaluated for prior history of thyroid hormone disturbance or thyroid drug consumption to assess previous thyroid dysfunction.

Collection of samples: Peripheral venous blood was drawn and allowed to coagulate at room temperature for 30–45 min, followed by centrifugation at 2500Xg for 15 min. All serum samples were stored at -700C and kept under these conditions until chemical analysis was performed.

Parameters assay

Anti-CCP antibodies assay: Sera were analyzed for Anti-cyclic-citrullinated peptide antibodies (anti-CCP) by ELISA (Inova Diagnostics, San Diego, CA, USA) with a cutoff value of 60 U/ml.

Serum TSH estimation: Estimation of serum TSH was done by chemiluminescence immunoassay method in Cobas 6000 (Roche Diagnostics). Within run %CV and Across runs were −1.1 to 3.0 % CV, and −3.2 to 7.2 % CV respectively. TSH value varied between 0.3 and 4.0 µIU/ml considered normal reference range of the study population.

Serum free T4 (fT4) and free T3 (fT3) estimation: Serum fT4 and fT3 estimationwere performed using chemiluminescent immunoassay (CLIA) method in Cobas 6000 (Roche Diagnostics) with reference range 0.7–1.8ng/dl for fT4 and 2.57–4.43 pg/ml for fT3. Within run % CV and across runs were −0.8 to 2.3 % CV, and −3.2 to 7.2 % CV considered for fT4 and−1.2 to 2.1 % CV, and −3.0 to 7.4 % CV considered for fT3.

Then thyroid dysfunction was diagnosed among RA cases based on evaluation of thyroid hormones,[6] as followed -

Overt hypothyroidism: TSH >3.6 and fT4<0.7

Subclinical hypothyroidism: TSH>3.6 with normal range of fT4

Overt hyperthyroidism: TSH<0.3 and fT4>1.8or fT3>4.43

Subclinical hyperthyroidism: TSH < 0.3 with normal range of fT4 and fT3

Euthyroid: normal range of TSH and fT4

Among these study population having thyroid dysfunction, Anti TPO antibody measurement was done.

Anti-TPO antibody: Anti-TPO antibody was also determined chemiluminescent immunoassay (CLIA) method in Cobas 6000 (Roche Diagnostics) with an optimum cut-off level of 50 IU/ml.[14,15] AITD was defined by positive anti-TPO and the presence or history of thyroid dysfunction.[16]

Statistical analysis: Data were entered using Microsoft Excel 2007.Then the data for biochemical analysis was subjected to standard statistical analysis such as Student's t test using the Statistical Package for Social Science (SPSS) 27 software. Before any analysis was done, normality was checked using the

Kolmogorov–Smirnov test, Q–Q, and P-P plots in continuous variables. Quantitative data with normal distributions including age, TSH and fT3 were described as mean ± standard deviation (SD) and all other data with non-normal distributions were reported as median (25–75th percentile). The difference of variables between cases and controls was assessed by using the Mann–Whitney U test for non-normally distributed data or the Student's T-test for normally distributed data. Where the chi-square test was inappropriate, the Fisher exact test was applied. For all tests 'p' value was considered to be significant if it was less than 0.05 at a confidence level of 95 %. The differences in the distribution were evaluated with Chi-square test. Correlations were evaluated with normal and Pearson's correlation tests. The values are expressed as mean ± SD.

RESULTS

The characteristics and their comparison among different groups of study population – Student's T-test and Odd Ratio

Baseline personal profile and clinical details of the study population are not statistically significant as shown in [Table 1]. It indicates that controls are baseline personal profile and clinical details matched with cases.

The number of participants with RF positive were 321 (47.9%) in cases. It was demonstrated that RA patients have a significantly higher level of ESR and CRP compared with the control group.

Table 1: Biochemical and anthropometric variables and their comparison between the controls and RA patients.

Characteristics	Control	Cases	z/t/OR	p value
Number of participants (n)	592	671		
Age (years)	42.96 ± 10.32	43.46 ± 9.29	- 1.42	0.162
Sex Male Female	 288 (48.6) 302 (51.4)	 340 (50.7) 331(49.3)	 1.92	 0.092
Demographic data Urban background Rural background	 294 (49.7) 298 (50.3)	 332 (49.5) 339 (51.5)	 1.45	 0.172
Duration of RA disease (year)		6.0 (3.0–11.0)		
Pain in joint		5.0 (0.0–12.0)		
Swelling of joint		3.0 (0.0–10.0)		
ESR (mm/h)	9.28 (6.0–13.2)	28.5 (10.0–51.0)	- 9.2	<0.001*
CRP (mg/L)	3.0 (2.5–4.0)	15.0 (8.0–38.0)	-7.2	<0.001*
RF positive		321 (47.9)		

Data are expressed as numbers (group percentages in parentheses) for categorical variables and mean values ± SD for continuous variables; Median (25th–75th percentile); RF Rheumatoid Factor; OR odd Ratio; p value < 0.05 considered statistically significant

3.2 Comparisons of serum TSH, fT4 and fT3 between cases and controls - Mann–Whitney U test and Odd Ratio

In [Table 2] it was demonstrated that RA patients have a significantly higher level of TSH, fT3 and fT4 compared with the control group.

Table 2: Comparisons of serum TSH, fT4 and fT3 between cases and controls.

Thyroid parameters	Controls (n = 592)	Cases (n = 671)	z/t/OR	p value
Serum TSH (µIU/ml)	2.4 (1.8 - 3.2)	3.1 (2.3 ± 3.9)	- 2.6	0.031
fT4 (ng/dl)	1.2 (0.9–1.4)	1.0 (0.7–1.3)	- 0.8	0.018
fT3 (pg/ml)	2.3 ± 1.3	3.9 ± 1.6	-4.8	0.092

Data are expressed as numbers mean values ± SD for continuous variables; Median (25th–75th percentile)

Frequency of thyroid dysfunctions among cases and controls - Mann–Whitney U test and Odd Ratio

The number of controls and cases with thyroid dysfunction were 107 (18%) and 248 (37%), respectively [Table 3 & Figure 1]. A significant association was found between RA disease and thyroid dysfunction which thyroid dysfunction was twice as common in RA patients as in controls (OR = 2.07, 95% CI: 1.42– 3.20; p-value > 0.001). As presented in [Table 2], the most common thyroid dysfunction was overt hypothyroidism. Only hypothyroidism was associated with RA disease and there was no significant association between other forms of thyroid dysfunction and RA.

Table 3: Frequency of thyroid dysfunctions among cases and controls

Thyroid functions	Cases (n = 671)	Controls (n = 592)	Unadjusted Odd Ratio (95% CI)	p-value
Euthyroid	423 (63%)	485 (82%)	0.46 (0.30–0.70)	< 0.001*
Overt hypothyroidism	161 (24%)	71 (12%)	2.27 (1.39–3.69)	0.008*
Subclinical hypothyroidism	60 (9%)	18 (3%)	1.39 (0.71–2.72)	0.012*
Overt hyperthyroidism	13 (2%)	12 (2%)	4.00 (0.44–36.04)	0.152
Subclinical hyperthyroidism	14 (2%)	6 (1%)	0.99 (0.98–1.00)	0.098

* The difference was statistically significant with the p-value <0.05; CI Confidence Interval

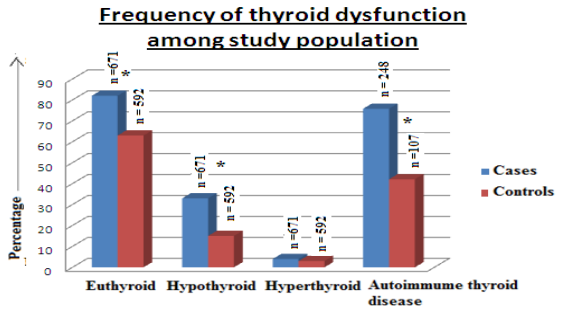

Figure 1: Frequency of thyroid dysfunctions among cases and controls. * The difference was statistically significant with the p-value <0.05

Frequency of Autoimmune thyroid disease among cases and controls with thyroid dysfunction - Mann–Whitney U test and Odd Ratio

In [Table 4] it was demonstrated that RA patients have a significantly higher level of Anti-TPO antibody compared with the control group (OR = 4.6, 95% CI: 1.70–4.13; p-value < 0.001).

Table 4: Comparisons of serum Anti-CCP, Anti-TPO and Anti-MCV between cases and controls

Parameters	Control (n = 107)	Cases (n = 248)	z/t/OR	p value
Anti-CCP (U/ml)		15.9 (2.2–185.5)		
Anti-TPO (IU/ml)	8.9 (5.0–25.0)	17.3 (6.4–157.0)	- 4.6	0.028
Anti-MCV (IU/ml)		47.1 (11.0–302.5)		

Table 5: Frequency of Autoimmune parameter among cases and controls with thyroid dysfunction

Parameters	Control (n = 107)	Cases (n = 248)	Unadjusted Odd Ratio (95% CI)	p value
AITD		238 (96%)		
Anti-TPO (IU/ml)	39 (36.44%)	143 (57.46%)	- 2.69 (1.70–4.13)	0.008
Anti-MCV		197 (79.4%)		

Anti-TPO = Thyroid Peroxidase Antibodies; Anti-MCV = anti-mutated-citrullinated vimentin autoantibodies; Anti-CCPanti-cyclic citrullinated peptides

Anti-TPO was significantly higher in 39 (36.44%) controls, and 143 (57.46%) cases and it was significantly more common in RA patients (OR = 2.69, 95% CI: 1.70–4.13; p-value 0.008). [Table 5]

Table 6: Frequency of Autoimmune thyroid disease among cases and controls with thyroid dysfunction

Parameters	Control (n = 107)	Cases (n = 248)	Unadjusted Odd Ratio (95% CI)	p value
AITD	45 (42.1%)	188 (75.8%)	- 2.69 (1.70–4.13)	0.008

Then [Table 6 and Figure 1] was shows that AITD was 2.87 times more common in RA patients (75.8%) than that in controls (42.1%) (OR = 2.87, 95% CI: 1.62–4.73; p-value < 0.001).

DISCUSSION

The relationship between RA and thyroid dysfunction has been taken into account since the 1960s when an association between RA and Hashimoto's thyroiditis based on the common underlying role of autoimmunity was found.[17,18] The prevalence of thyroid dysfunction with and without AITD is estimated to be between 6 and 33.8% respectively in RA patients.[19] However, it is worthy of mention that thyroid dysfunction, AITD, and anti-TPO positivity prevalence varies among RA patients based on geographical locations as instance prevalence of AITD among RA patients can range from 0.5% in Morocco,[20] to 27% in Slovakia,[21] and anti-TPO differ from 5%,[22] in Egypt to 37% in Italy.[23]

Since in early research the control group was absent, some recent studies have investigated the association between thyroid hormone dysfunction and AITD in RA patients.[24] Although Sara McCoy et al. found no difference in prevalence or development of hypothyroidism in RA patients, Prakash Joshi et al., in a survey enrolling 52 RA patients, estimated hypothyroidism was 3.5 times more prevalent compared with the general population.[25,26] Since a firm consensus is not reached on this matter and the association also was not well studied in the Eastern Indian population, this case–control study enrolling 671 RA and 592 control population have been designed to investigate this issue. This study demonstrated a significant association between thyroid dysfunction and RA which was twice as common in RA patients as in controls. The prevalence of patients with thyroid dysfunction were 18% in controls and 37% in cases which hypothyroidism was the most prevalent form including 15% and 33% of thyroid dysfunction. Like most of the previous research, we found significant association with hypothyroidism but not for hyperthyroidism. Nevertheless, Qian Li et al. found both hypo and hyperthyroidism were significantly prevalent in RA patients than controls among the Chinese population,[27] but hyperthyroidism is not associated with in our participants. It should also be mentioned that several studies only consider overt hypothyroidism and did not include the subclinical stage in their evaluation, yet some studies included both stages. In most of these studies, overt hypothyroidism was the most common thyroid dysfunction,[19,28-30] however, several of them showed

subclinical hypothyroidism as the most common one,[17] while others found no significant difference between subgroups.[31] We concluded from the study that RA only associated with both overt as well subclinical hypothyroidism, 2.3 times more common among RA patients than controls. Moreover, recent studies have paid more attention to the prevalence of anti-thyroid antibodies positivity and AITD in RA patients. Xi-Feng Pan et al., in a meta-analysis, estimated that the presence of anti-TPO is 2.3 times more common in RA patients compared with healthy individuals. Although anti-thyroid autoantibodies were positively associated with RA disease in Asian and African populations, no significant association was detected in most of the studies conducted in America and Europe. The reason for this contrast might lie in geographical genetic, and environmental differences or preliminary studies to find its real association.[30] In this study, we also estimated that the prevalence of anti-TPO positivity was 15.0% of controls and 32.0% of cases and it was 2.69 times greater in RA patients compared with controls.

The association between AITD which an organ-specific autoimmune disease, and systematic autoimmune diseases like systemic lupus erythematous, primary Sjögren's syndrome, and especially RA was shown in several studies which could be explained by the similar underlying autoimmune pathogenesis and possible genetic susceptibility.[24] Despite the finding that AITD was more common among RA patients with thyroid dysfunction compared to healthy individuals, some studies found this difference to be not statistically significant.[19] Whereas in our analysis, AITD was 2.87 times more prevalent in RA patients compared with controls with thyroid dysfunctions which was statistically significant (75.8 vs. 42.1%). Although seronegative thyroiditis, which is characterized by thyroid dysfunction without positive tests for thyroid autoantibodies and a hypoechoic pattern of the thyroid parenchyma at ultrasound, was not included in this study, it does not seem to have a significant impact on our analysis because of low prevalence of this form of thyroiditis (~ 5%).[32]

CONCLUSION

This study concluded that RA disease was associated thyroid dysfunction especially AITD among the Eastern Indian population like several other populations.

Limitation of the Study

Nonetheless, this research is subject to several limitations such as lack of measuring other kinds of anti-thyroid antibodies and detailed factors affecting the prevalence of thyroid abnormality in RA patients, for instance body mass index, smoking (although it is notable that most of the enrolled patients were middle-aged women and smoking is scarce in this demographic of Eastern Indian population), lifestyle, genetic background, and so on; hence, it leaves room for further studies. Another limitation of the study is that, it was conducted at a single center, it has a retrospective nature of the study design and the study has performed with low study population.

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