ORIGINAL ARTICLE

Prevalence and Clinical Use of Anti-Thyroid Antibodies in RA Patients: A Prospective Case-Control Study

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Abstract

Aim: To evaluate the prevalence of anti-thyroid antibodies in a cohort of rheumatoid arthritis (RA) patients from south India and their clinical use.

Methods: The prospective case-control study, conducted for 3 consecutive months in a tertiary care hospital based in India, evaluated 103 RA patients (active group) and 36 age-matched healthy controls without the disease. Both the control and active groups were compared for thyroid autoantibodies, and the clinical evaluation included assessment of swollen joint counts (SJC), tender joint counts (TJC), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), pain scale, disease activity score (DAS), rheumatoid factor (RF), anti-nuclear antibody (ANA) and anti-cyclic citrullinated peptide (anti-CCP). The active group subjects were further subdivided into RA patients with and without hypothyroidism, and were compared for normal and abnormal levels of thyroid autoantibodies and the variations were statistically analysed.

Results: The corresponding mean age of the subjects belonging to the active and control groups were 47.09±11.29 and 41.03±11, with a female to male ratio of 1:0.12 and 1:0.29 respectively. Among the various thyroid autoantibodies compared between the active and control groups, a significant correlation (P=0.00936) was observed for anti-TTG antibodies. Also, the study has noted a significantly elevated level of anti-TPO antibodies in RA patients with hypothyroidism compared to the group without hypothyroidism (P=0.0074).

Conclusion: A significantly increased level of anti-TPO antibodies was noted in RA patients with hypothyroidism.

Introduction

RA is a chronic inflammatory autoimmune disorder that affects approximately 0.5-1% of the population.[1] The increased prevalence of thyroid diseases noted in patients suffering from RA has been well established.[2-5] The association and the probability for existing a common etiology for both the diseases have not been fully understood, however some literature studies have shown that they share some common genes, such as *CD40, CTLA4, HLA* gene complex, and *PTPN22*, which may increase the risk of disease development.[6–10] The risk for developing hypothyroidism is higher in patients receiving treatment for RA.[11] As per the literature evidence, the prevalence of hormonal dysfunction and/or autoimmune thyroid disease (ATD) noted in RA patients ranges between 6% to 33.8%, with more preponderance in female patients.[12] Many previous studies have shown an increased prevalence of anti-thyroid antibodies in RA patients. For instance, a study by Atzeni et al. has reported a prevalence of 37% and 23% for anti-thyroperoxidase (TPOAb) and anti-thyroglobulin antibody (TgAb) positivity among Italian RA patients respectively.[10] Similar findings have also been noted in Indian population.[13]

In addition, patients with thyroid dysfunction and RA are more prone to develop cardiovascular diseases.[14] Such patients may possess elevated risk for exacerbation or precipitation of musculoskeletal diseases, as there is an increased probability for masking original symptoms of RA by symptoms and features of hypothyroidism.[14] Hence it is necessary to elucidate the role of these antibodies and their usefulness in clinical evaluation of RA patients.[15] The present study evaluated the prevalence and clinical use of anti-thyroid antibodies in RA patients.

Material and Methods

The prospective case-control study, conducted at a tertiary centre between February and April, 2016, recruited subjects fulfilling 2010 ACR/EULAR Classification Criteria for Rheumatoid Arthritis into active group and age-matched healthy subjects without the disease into the control group. Other inclusion criterion considered was age group between 18 and 65. The exclusion criterion was patients with a history of overlap connective tissue diseases. Demographic and clinical characteristics such as age, gender, smoking, alcohol consumption, occupation, duration of rheumatoid arthritis and treatment history were collected. Clinical evaluation included assessment of tender joint counts (TJC), swollen joint counts (SJC), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), pain scale, disease activity score (DAS), rheumatoid factor (RF), antinuclear antibodies (ANA) and anti-cyclic citrullinated peptide (anti-CCP).

Active and control groups were compared for thyroid autoantibodies namely anti-thyroid peroxidase (anti-TPO), anti-tissue transglutaminase antibody (anti-TTG), and thyrotropin (TSH) receptor. The active group subjects were further evaluated for their thyroid disease status and they were subclassified into RA patients

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with hypothyroidism and RA patients without hypothyroidism. The two sub-groups were compared for normal and abnormal levels of thyroid autoantibodies and the variations were statistically analyzed. Medcalc was the software used for the statistical analysis.

Results

Out of the 139 selected participants, 103 served as active subjects and 36 as age-matched controls. The mean age of the subjects belonging to the active and control groups were 47.09±11.29 and 41.03±11.42 respectively. The corresponding female to male ratio noted in the groups were 1:0.12 and 1:0.29. None of the subjects were consuming alcohol or tobacco products. Among the103 subjects, 11 were employed and 92 were unemployed. Duration of RA ranged from 6-240 weeks with an average of 36 weeks in the active group. The corresponding TJC and SJC noted were both 4. The mean ESR and CRP noted were 60 and 7 respectively. The average pain scale score noted was 10 (range 0-90). The mean DAS of 28 joints with 3 variables was 4.26±1.24. Among the 103 active patients, RF and anti-CCP positivity were noted in 63 and 59 subjects respectively (Table 1).

Table 1: Evaluation of clinical and demographic parameters for active and control groups

Parameters	Active	Control
Age (mean ±SD)	47.09 ± 11.29	41.03±11.42
Gender (F/M)	92/11	28/8
Smoking	0	
Alcohol	0	
Occupation (Y/N)	11/92	
Duration of RA, median (range)	36 (6-240)	
TJC, median (range)	4(0-18)	
SJC, median (range)	4(0-12)	
ESR, median (range)	60 (10-140)	
CRP, median (range)	7 (0-98)	
Pain scale, median (range)	10 (0-90)	
DAS 28(3) (mean ±SD)	4.26±1.24	
RF (positive/negative)	63/40	
Anti-CCP (positive/ negative)	59/44	

The thyroid autoantibodies and their levels compared between RF-positive and RF-negative patients were: anti-TPO≤35, anti-TPO>35, anti-TTG≤10, anti-TTG>10, TSH-receptor≤4.5 and TSH-receptor>4.5 (Table 2, Figure 1). No significant difference was observed between anti-TPO≤35 and anti-TPO>35, anti-TTG≤10 and anti-TTG>10 (P=0.6629), and also between TSH-receptor ≤4.5 and TSH-receptor >4.5 (P=1) (Table 2). However, comparison of anti-TTG≤10 and anti-TTG>10 between active and control groups was found to be highly significant (P=0.00936, Table 3). Whereas, no significant difference was observed between the two groups on comparison of anti-TPO ≤35 and anti-TPO >35, and TSH-receptor ≤4.5 and TSH-receptor >4.5. In addition, the comparison of these autoantibodies with respect to anti-CCP status did not show any significant findings (not shown in tables).

Table 3: Comparison of active and control groups for thyroid autoantibodies

Thyroid autoantibodies	Active	Control	P value
Anti-TPO≤35	87	32	0.5938
Anti-TPO>35	16	4	
Anti-TTG ≤10	67	32	0.00936
Anti-TTG>10	36	4	
TSH-receptor≤4.5	102	36	1
TSH-receptor>4.5	1	0	

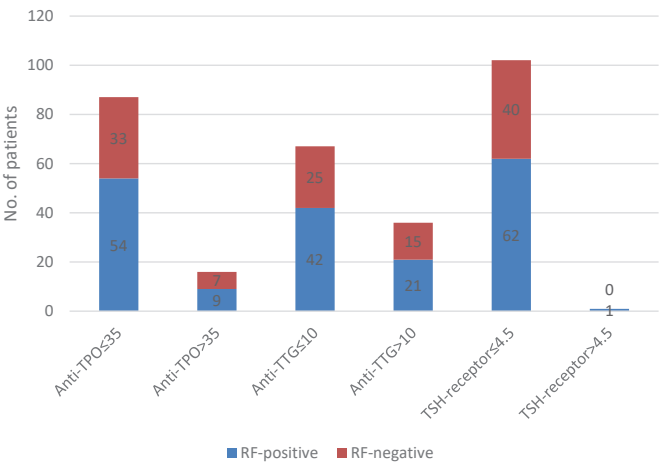

Fig. 1: Distribution of thyroid disease markers with reference to RF status

Twenty cases (19.42%) out of 103 patients with hypothyroidism were on thyroxine treatment. Significantly elevated anti-TPO antibodies were found in RA patients with hypothyroidism than those without hypothyroidism (P= 0.0074). But anti-TTG levels did not significantly differ between the two groups (P=1, Table 4).

There was no incidence of diabetes in RA patients with hypothyroidism and some incidence had been observed in RA patients without hypothyroidism. However, there was no statistically significant difference between the groups, suggesting that there is no relationship between hypothyroidism and diabetes (P >0.05, Table 5).

Discussion

Comparison of thyroid autoantibodies between patients with and without RA has demonstrated that anti-TTG was significantly higher in subjects with RA compared to controls (P=0.00936). In concurrence with the present study findings, Spadaro et al. have reported that serum anti-TTG levels were significantly higher in RA (P<0.0001) than controls.[16] The results of the present study are in agreement with the results noted in Turkish (15.9% and 12.3%), Polish (15 and 12%) and Colombian (37.8 and 20.8%) RA populations.[1,16,17] Further studies involving larger sample size may help to establish the association between ant-TTG and RA.

The present study has also evaluated the association of hypothyroidism

Table 2: Comparison of RF-positive and RF-negative subjects for thyroid autoantibodies

Thyroid autoantibodies	RF positive	RF negative	n (%)	P value
Anti-TPO ≤35	54	33	87 (84.46)	
Anti-TPO >35	9	7	16 (15.53)	0.6629
Anti-TTG ≤10	42	25	67 (65.04)	
Anti-TTG >10	21	15	36 (34.95)	0.6629
TSH-receptor ≤4.5	62	40	102 (99.02)	
TSH-receptor >4.5	1	0	1 (0.97)	1

Table 4: Comparison of RA patients with and without hypothyroidism for anti-TPO and anti-TTG levels

Thyroid autoantibodies	RA without hypothyroidism n (%)	RA with hypothyroidism n (%)	P value
Anti-TPO ≤35	74 (89.15)	13 (65)	0.0074
Anti-TPO >35	9 (10.84)	7 (35)	
Anti-TTG ≤10	54 (65.06)	13 (65)	1
Anti-TTG >10	29 (34.93)	7 (35)	

Table 5: Comparison of RA patients with and without hypothyroidism for incidence of diabetes

Rheumatoid arthritis	DM (+) n (%)	DM (-) n (%)	n
With hypothyroidism	0 (0)	20 (100)	20
Without hypothyroidism	7 (8.43)	76 (91.56)	83
P value 0.3405			

and thyroid autoantibodies with RA. The study has found significantly elevated levels of anti-TPO antibodies in RA patients with hypothyroidism compared to those without the disease (P= 0.0074). In concurrence to the present findings, Przygodzka et al. underscored the need for screening of anti-TPO antibodies as the marker of ATD, especially in female RA patients. Similarly, Elattar et al. have found a significant positive correlation between TSH levels and RA disease activity parameters. Moreover, Comparison of RA patients with controls demonstrated a significant difference in the levels of TSH ($P < 0.05$), anti-TPO antibodies ($P < 0.05$), and anti-Tg antibodies ($P < 0.05$).[18]

A cross-sectional, analytical study conducted by Roldán et al. among 800 consecutive Colombian patients with RA has reported a corresponding prevalence ranges of 6% to 31% and 5% to 37% for anti TG and anti TPO antibodies. The study has also reported a positive association between ATD and type 2 diabetes (P=0.016).[17] This is in stark contradiction to the present study result reporting no relation between hypothyroidism and diabetes ($P > 0.05$). Dessein et al. have found that subclinical hypothyroidism is associated with the development of insulin resistance in RA patients.[19] However, the present study has not evaluated whether the incidence of diabetes in the study participants was due to insulin resistance. Moreover, the limited sample size would have influenced the study findings. It could also be due to the absence of lifestyle habits like alcohol and tobacco consumption in the study population.

It has been established that a combination of factors including diet, lifestyle habits, environmental exposures and genetic factors plays a major role in causing autoimmune diseases. Since majority of the Indian females do not consume alcohol and tobacco products, the effect of these lifestyle habits on the present study population is trivial.

However, the association between thyroid dysfunction and RA is very controversial. Some studies have reported a reduced prevalence of thyroid autoantibodies in RA patients. The study by Andonopoulos et al. conducted in 70 RA patients and age-matched controls have concluded no association between thyroid disorders and serologic RA profile.[20] As per the literature evidence, there is no study comparing the prevalence and clinical use of anti-thyroid antibodies in RA patients from Indian settings, hence the present study can be considered as first of its kind evaluating the association.

The relatively small size is one of the major limitations of the study. A larger and more diverse sample size would have further strengthened the study findings.

Conclusion

The present study reports a significantly increased level of anti-TPO antibodies in RA patients with hypothyroidism. The study warrants further research to establish the use of anti-TPO antibodies as a marker to monitor the course of ATD in RA patients.

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