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ORIGINAL ARTICLE

Prevalence of Thyroid Dysfunctions in Patients with Rheumatoid Arthritis at Tertiary Care Hospital

Shafique Rehman Arain,[1] Nand Lal Seeran,[2] Nasrullah Aamer,[3] Muhammad Tariq Karim,[4] Furqan Khan,[1] Assadullah Dahani[1]

1. Department of Rheumatology. Medical Ward-6. Jinnah Postgraduate Medical Center, Karachi.
2. Department of Gastroenterology. Liaquat University of Medical and Health Sciences, Hyderabad.
3. Department of Medicine. Peoples University of Medical and Health Sciences, Shaheed Benazirabad, Nawabshah.
4. Head of Research Evaluation Unit. College of Physicians and Surgeons, Karachi.

Correspondence to: Dr. Shafique Rehman Arain, Email: drshafiq123@gmail.com, ORCiD: 0000-0003-0404-7335

ABSTRACT

Objective: To determine the burden of thyroid dysfunctions in Rheumatoid Arthritis (RA) patients attending tertiary care hospital of Karachi, Pakistan.

Methods: A cross-sectional study was conducted at rheumatology clinic of a Jinnah Post Graduate Medical Centre in Karachi, Pakistan from April 2019 to January 2021. All diagnosed cases of RA having seronegative or seropositive RA were consecutively enrolled. Clinical records and laboratory data of these patients were collected along with outcome variables.

Results: Of 136 patients, thyroid abnormality was observed in 56 (41.2%) patients. In particular, 80 (58.8%) had normal, 8 (5.9%) had hypothyroidism, 14 (10.3%) had hyperthyroidism, 32 (10.5%) had subclinical hypothyroidism, and 2 (1.5%) had subclinical hyperthyroidism. A significantly lower hemoglobin levels (p-value <0.001), mean corpuscular volume (p-value 0.011), total leucocyte count (p-value 0.004), and platelet counts (p-value 0.040) were observed in patients with thyroid abnormality than those without thyroid abnormality. Furthermore, a significantly lower urea (p-value <0.001) and creatinine levels (p-value <0.001) were also observed among patients with thyroid abnormality than those without thyroid abnormality.

Conclusion: In patients with RA, thyroid dysfunction has been shown to be highly prevalent. Subclinical hypothyroidism, the most common thyroid disorder and obvious hyperthyroidism were observed.

Keywords: Hyperthyroidism, Hypothyroidism, Rheumatoid Arthritis, Thyroid Dysfunction.

INTRODUCTION

Rheumatoid Arthritis (RA) is a chronic and systemic autoimmune disease which can result in constant inflammatory polyarthritis and continuous joint destruction, leading to damaged mobility and increased disability.[1] Even though RA affects mainly joints, extra-articular involvement can occur in approximately 40% of patients.[2] In addition to articular and extra-articular manifestations, various comorbidities can complicate the course of disease.[3]

Patients with RA are at increased risk of diabetes, vasculitis, lung diseases and hearing loss, probably due to autoimmunity, compared with the general population.[4-7] Other common comorbidities among patients with RA are cardiovascular events, different types of cancers, depression, and so on.[3] These comorbid diseases can affect the long-term prognosis and may decline the functional status, and also life span of the patients.[3]

It is thought that individuals from risk groups (of thyroid diseases development) should be screened i.e., women with family history of thyroid diseases, with previous thyroid dysfunction, with symptoms suggestive of hyperthyroidism or hypothyroidism, with abnormalities in physical examination of the thyroid gland, type 1 diabetes and a history of other autoimmune diseases.[6] As RA and thyroid issues both are highly prevalent in our part of the world and the published studies have reported higher prevalence of thyroid issues in RA patients, this study is therefore performed to investigate and observe the frequency and most common pattern of thyroid dysfunction in patients with RA.

METHODS

This observational study was conducted at the Rheumatology department of the Jinnah Post Graduate Medical Centre, Karachi, Pakistan from April 2019 to January 2021. Ethical approval was obtained from the ethical review committee of the institute prior conducting of the study.

This study included 136 patients of Sero-negative or Sero-positive RA. Data were prospectively collected from all the patients of age >16 years, diagnosed according to the 2010 American College of Rheumatology/European League Against Rheumatism classification criteria for RA. All the patients who were already taking medications for thyroid dysfunctions, patients had thyroid surgery or iodine therapy, patients with mixed connective tissue disorder, overlap syndromes, malignancy were excluded.

The purpose and procedure of the study was explained to each patient and an informed consent was taken from all the patients. Detailed history including risk factors and family history of thyroid diseases were obtained, physical examination especially, examination of the musculoskeletal system, laboratory investigations, including thyroid stimulating hormone, Free T3 and Free T4, Anti-thyroglobulin antibodies, Thyro-peroxidase antibodies, erythrocyte sedimentation rate, C-Reactive protein was done in all patients and reported. Demographics variables like age, gender and menstrual status were noted. Along with these parameters disease activity scoring was also obtained by mean of clinical disease activity index (CDAI).

Blood sample was collected from all the patients in yellow top bottle and reporting was done from same laboratory. Results were collected and filled in pre-designed proforma.

Normal ranges for free T3 (fT3) is 100 to 200 ng/dL, free T4 (fT4) is 0.7 to 1.9 ng/dL, thyroid stimulating hormone is 0.4 to 4.05 mU/L, thyroid peroxidase antibody level (TPO) is <9 IU/mL and thyroid binding globulin is 1.1 to 2.1 mg/dL

Hypothyroidism was defined as high levels of TSH, i.e> 4.05 mU/l, Low levels of fT3 of <100 ng/dL or low levels of fT4 <0.7 ng/dL and high levels of TPO >10 IU/mL. Hyperthyroidism was defined as low levels of TSH, i.e<0.4 mU/l, high levels of fT3 of >200 ng/dL or high levels of fT4 >1.9 ng/dLm and normal TBG. Subclinical Hypothyroidism was defined as high levels of TSH, i.e> 4.05 mU/l while normal levels of fT3 and fT4. Sub-clinical Hyperthyroidism was defined as normal levels of TSH, while high levels of fT3 > 4.05 mU/l or fT4 >1.9 ng/dL.

Statistical data analysis was performed using SPSS statistical software, version 21.0. Mean ± SD were calculated for continuous variables where frequencies and percentages were used to see the pattern of thyroid status in RA patients. Statistical significance was determined via Independent t-test and Chi-square/Fisher-Exact test. The p-value ≤0.05 was taken as significant.

RESULTS

Of 136 patients, the mean age of the patients was 38.66± 10.15 years. Females were predominantly higher as compared to males, i.e., 126 (92.6%) and 10 (7.4%) respectively. The mean age was significantly higher among patients without thyroid abnormality as compared to those with thyroid abnormality, i.e., 40.40 ±9.67 and 36.18 ±10.38 (p-value 0.016). Moreover, thyroid abnormality was significantly higher among males as compared to females, i.e., 8 (80%) and 48 (38.1%) respectively.

Thyroid status showed that 80 (58.8%) had normal, 8 (5.9%) had hypothyroidism, 14 (10.3%) had hyperthyroidism, 32 (10.5%) had subclinical hypothyroidism, and 2 (1.5%) had subclinical hyperthyroidism (Figure 1). Overall, thyroid abnormality was observed in 56 (41.2%) patients.

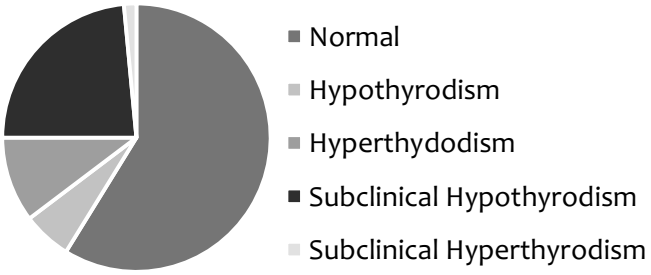

Figure 1: Thyroid status in patients with rheumatoid arthritis (n=136)

The treatment profile showed that hydroxychloroquine and Methotrexate were used by 136 (100%) whereas prednisolone by 94 (69.1%) patients. There were 42 (30.9%) patients who were using Disease-modifying anti-rheumatic drugs whereas 94 (69.1%) were using A+D steroids. RA factor was positive in 124 (91.2%) patients. Moreover, anti-cyclic citrullinated peptide (CCP) was observed in36 (26.5%) and antinuclear antibodies (ANA) in 2 (1.5%) patients. The comparisons of clinical characteristics are shown in detailed in table 1. A significantly lower hemoglobin levels, mean corpuscular volume, total leucocyte count, and platelet count were observed in patients with thyroid

Table 1: Comparison of baseline and clinical characteristics with thyroid abnormality (n=136)

	Total	Thyroid Abnormality		p-value
		Yes	No	
Age, years (Mean ±SD)	38.66 ±10.15	36.18 ±10.38	40.40 ±9.67	0.016˜
≤40	98	46 (46.9)	52 (53.1)	0.028^
>40	38	10 (26.3)	28 (73.7)	
Gender				
Male	10	8 (80)	2 (20)	0.010*
Female	126	48 (38.1)	78 (61.9)	
Treatment				
DMARDS	42	18 (42.9)	24 (57.1)	0.790^
A+D + Steroids	94	38 (40.4)	56 (59.6)	
RA Factor				
Positive	124	52 (41.9)	72 (58.1)	0.563^
Negative	12	4 (33.3)	8 (66.7)	
Anti CCP				
Positive	36	22 (61.1)	14 (38.9)	0.005^
Negative	100	34 (34.0)	66 (66.0)	
TSH				
Normal	80	0 (0)	80 (100)	<0.001*
Decrease	16	16 (100)	0 (0)	
Increase	40	40 (100)	0 (0)	
FT3				
Normal	96	26 (27.1)	70 (72.9)	<0.001^
Decrease	26	20 (76.9)	6 (23.1)	
Increase	14	10 (71.4)	4 (28.6)	
FT4				
Normal	84	20 (23.8)	64 (76.2)	<0.001*
Decrease	10	10 (100)	0 (0)	
Increase	42	26 (61.9)	16 (38.1)	
Prednisolone				
Yes	94	38 (40.4)	56 (59.6)	0.790^
No	42	18 (42.9)	24 (57.1)	
HCQ				
Yes	136	56 (41.2)	80 (58.8)	-
No	-	-	-	
MTX				
Yes	136	56 (41.2)	80 (58.8)	-
No	-	-	-	

All data presented as number (%)

˜Independent t-test and ^Chi-square/*Fisher-Exact test applied, p-value ≤0.05 considered as significant

abnormality than that of those without thyroid abnormality, i.e., 36.18 ±10.38 vs. 40.40 ±9.67 (p-value <0.001), 60.58 ±36.31 vs. 77.68 ±9.87 (p-value 0.011), 5.18 ±3.44 vs. 7.60 ±2.87 (p-value 0.004), and 229.67 ±148.53 vs. 294.05 ±93.15 (p-value 0.040). Furthermore, a significantly lower urea and creatinine levels were also

Table 2: Mean difference of laboratory parameters with respect to thyroid abnormality

		Thyroid Abnormality		
	Total	**Yes**	**No**	**p-value**
Hb, g/dl (n=62)	9.50 ±3.38	36.18 ±10.38	40.40 ±9.67	<0.001
MCV (n=58)	70.60 ±25.69	60.58 ±36.31	77.68 ±9.87	0.011
TLC (n=62)	6.67 ±3.29	5.18 ±3.44	7.60 ±2.87	0.004
Platelet (n=74)	269.12 ±120.75	229.67 ±148.53	294.05 ±93.15	0.040
ESR (n=56)	57.64 ±28.58	66.67 ±35.66	50.56 ±19.78	0.036
SGPT (n=46)	17.52 ±11.58	16.67 ±13.63	18.07 ±10.29	0.693
Urea (n=40)	17.81 ±11.45	10.01 ±9.42	22.01 ±10.29	<0.001
Cr (n=44)	0.63 ±0.29	0.45 ±0.37	0.74 ±0.17	<0.001

Independent t-test applied, p-value ≤0.05 considered significant

Table 3: Mean difference of TSH, FT3, and FT4 with respect to thyroid abnormality

		Thyroid Abnormality		
	Total	**Yes**	**No**	**p-value**
TSH, mIU/l (n=136)	3.04 ±3.12	5.26 ±3.78	1.57 ±0.90	<0.001
FT3 (n=114)	2.57 ±1.43	2.61 ±1.93	2.53 ±0.94	0.769
FT4 (n=134)	2.62 ±1.54	3.21 ±2.84	2.21±1.14	0.027

Independent t-test applied, p-value <0.05 considered significant

observed among patients with thyroid abnormality than that of those without thyroid abnormality, i.e., 10.01 ±9.42 vs. 22.01 ±10.29 (p-value <0.001) and 0.45 ±0.37 vs. 0.74 ±0.17 (p-value <0.001). (Table 2) A significantly higher TSH level and FT4 level was observed among patients with thyroid abnormality than that of those without thyroid abnormality, i.e., 5.26 ±3.78 vs. 1.57 ±0.90 (p-value <0.001) and 3.21 ±2.84 vs. 2.21±1.14 (p-value 0.027) respectively. (Table 3)

DISCUSSION

The findings of the current study showed that frequency of thyroid dysfunction was higher particularly subclinical hypothyroidism. This finding was remarkably higher compared to a previous study conducted by Emamifar et al in 2017 in Denmark in thyroid dysfunction was reported in sixteen percent patients only.[9]

Autoimmune thyroid diseases are the most prevalent organ-specific autoimmune diseases and affect 2-5% of the general population. Several studies have shown their higher prevalence in patients with some RA.[7,8]

Previous study showed significant increase in thyroid disorder in rheumatic disease (8%) and thyroid autoantibodies were found to be significantly higher in patients with rheumatoid disease as compared to healthy controls. Additionally, thyroid disorders were observed more frequently in patients with rheumatoid disease than in the healthy controls.[10] The significant higher number of thyroid disorders detected in rheumatic disease is due possibly to genetic, environmental, and hormonal role play. An association between RA and thyroid dysfunction with or without autoimmune origin has been reported in six to thirty four percent patients with RA.[11] A hormonal dysfunction and/or autoimmune thyroid disease are present in six to thirty three percent patients with RA.[12-14]

There have been several proposed underlying mechanisms. In both autoimmune rheumatic diseases, both autoimmune thyroiditis and RA can be caused by auto-reactive T-cells, which can cause primary thyroid destruction, or Poly-B cell activation. Autoimmune thyroid disease is possible after thyrotropin production by activated or autoantibodies lymphocytes.[15] In the case of rheumatic disease human leukocyte antigen (HLA) haplotyping may also play another role in thyroid dysfunction pathogenesis.[16] In patients with RA and thyroid dysfunction, the link between HLA - DR2 and DR4 was also shown to be seronegative and seropositive, as were the HLA - DR2 and DR4 antigens.[17,18]The concomitant presence of these diseases is more frequent in women than men.[12,14,19] Clinical manifestation of these diseases is often proceeded by presence of characteristic organ specific antibodies that might occur in serum even a few years before symptom onset and making a diagnosis.[20] Age, duration and activity of RA, the presence of rheumatoid

factor and ANA have not been found to predispose to coexistence of these diseases.[12,14,19]

In the current study findings, a considerably lower hemoglobin levels, mean corpuscular volume, total leucocyte count, and platelet count were observed in patients with thyroid abnormality than that of those without thyroid abnormality. Furthermore, a considerably lower urea and creatinine levels were also observed among patients with thyroid abnormality than that of those without thyroid abnormality.

In this study, a considerably higher TSH level and FT4 level was observed among patients with thyroid abnormality than that of those without thyroid abnormality.

There were certain limitations in this study. Firstly, this was a single center study and was conducted in a limited number of sample size. Furthermore, certain important predictor variables like family history of thyroid disease, occupational risk factors, smoking, and environmental radiation exposure were not explored. Furthermore, in the current study, all patients were free of comorbidities. Individuals with comorbid conditions and RA should also be explored for thyroid dysfunction and its risk factors. Despite of these limitations, this study is of significance as the study has reported findings from the developing country Pakistan where RA and thyroid issues both are highly prevalent and studies determining the burden and associated factors of thyroid dysfunction is scarce. Further largescale multicenter studies are recommended that not only include the potential confounders that were not included in the study but also report the longitudinal findings like treatment outcome and health related quality of life of these patients.

CONCLUSION

In connective tissue disorder patients, thyroid dysfunction has been shown to be highly prevalent. Subclinical hypothyroidism, the most common thyroid disorder and obvious hyperthyroidism were observed. For the detection of thyroid abnormalities, regular screening of patients with connective tissue disorders is recommended.

ETHICAL APPROVAL: The study protocol was approved by the Institutional Review Board Committee JPMC, Karachi.

AUTHORS'CONTRIBUTION: SRA: Data collection, write up and literature search. NLS: Proof reading, write up and data interpretation. NA: Literature search and data analysis. MTK: Conceptualization of study design and data interpretation. FK: Data collection & interpretation. AD: Literature search and conceptualization of study design.

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