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Study of thyroid function in patients of rheumatic disorders

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Abstract

Background: A number of dysfunctions may affect the thyroid gland leading either to hyper- or hypothyroidism which are mediated by autoimmune mechanisms. Thyroid abnormalities may represent an isolated alteration or they may be the harbinger of forthcoming disorders as is the case of well-characterized polyendocrine syndromes. Also, they may precede or follow the appearance of rheumatic manifestations in patients affected with connective tissue diseases or rheumatoid arthritis.

Material and Methods: This observational prospective study was conducted in the patients attending Medicine department at a SAIMS Medical College & Hospital-Indore from November 2019 to November 2021. In rheumatology/medicine outpatient/wards diagnosed patients with rheumatic disorders, after considering exclusion and inclusion criteria, were consecutively included in the study.

Inclusion Criteria: Patients with rheumatic disorders. Patients consenting to be included in the study

Exclusion Criteria: Pregnancy, Children <12 years of age, Patients not consenting to be included in the study.

Conclusion: According to the available data, thyroid dysfunction seems more common in patients with rheumatic diseases than in the general population, though the high prevalence of autoimmune thyroid diseases in young or mid-aged women should be considered.

Keywords: Thyroid, Pregnancy, Rheumatic.

Introduction

Rheumatic disorder is a chronic systemic autoimmune disease characterized by a symmetrical inflammation of the synovium, resulting in tenderness and destruction of bone and cartilage in various joints, particularly the smaller parts of the hands and feet. Traditionally, autoimmune diseases like hypothyroidism and rheumatic disorders were considered separate disease entities, as the manifestations are, on the one hand, more organ specific (such as Hashimoto's thyroiditis), and on the other hand,

more systemic. In general, patients suffering from an autoimmune disease have a strong hereditary susceptibility for other autoimmune diseases and higher incidences of autoantibodies have been detected in their relatives[1]. The combination of rheumatic disorders and autoimmune thyroiditis is recognized[2]. The patients with rheumatic disorders usually present with eu-, hypo- or hyperthyroid manifestations, mediated by autoimmune mechanisms. Thyroid abnormalities may represent an isolated alteration or they may be the harbinger of forthcoming disorders as is the case of well-characterized polyendocrine syndromes. Also, they may precede or follow the appearance of rheumatic manifestations in patients affected with connective tissue diseases or rheumatoid arthritis. The mechanisms by which autoimmune thyroid disorders may be linked to systemic autoimmune diseases have not been fully unraveled yet; however alterations of common pathways are suggested by shared genetic variants affecting autoantigen presentation and regulation of the immune response. On the other hand, the higher prevalence of autoimmune thyroid disorders over rheumatic diseases compels the chance of a mere causal concomitancy in the same patient[3].Thus detection of thyroid involvement in different rheumatic diseases and to look into the rheumatic manifestations in the context of autoimmune thyroid diseases becomes essential. Prevalence rate of autoimmune mediated hypothyroidism is about 0.8 per 100 and 95% among them are women. People RA are more likely to develop autoimmune thyroiditis than the general population, and as the symptom of fatigue can easily be attributed to RA when it may actually be stemming from hypothyroidism, it is recommended that people with RA have their thyroid function and hormone levels regularly screened via testing TSH and free thyroxine (T4) levels[4].Because of the high prevalence of ATD and antithyroid auto antibodies, it is clinically important to screen patients with autoimmune rheumatic disorders for the presence of thyroid autoimmunity[5]

Due to the overlapping and nonspecific nature of symptoms, it is difficult to clinically uncover thyroidal illnesses in autoimmune conditions such as RA, SLE and Sjogren's syndrome. It is important to perform thyroid function tests in these patients. Thus, appropriate management of all co-morbidities is important for comprehensive patient care[6]. Thus, present study is an attempt to study the thyroid function in the rheumatic disorders.

Objective

To study clinical features of thyroid dysfunction in patients of rheumatic disorders. To investigate for thyroid dysfunction in patients of rheumatic disorders. To study the response to treatment in case of thyroid dysfunction in these patients.

Background

Historical note: That rheumatic features can be associated with thyroid disorders has been known for some time: for example, in 1873 Sir William Gull described two cases of 'A cretinoidal state supervening in Adult Women'; describing neck stiffness and joint pain; and early British reports were described by Doyle in 1993. In 1883 Coxwell described myopathy in a case of juvenile myxoedema - a 13-yearold girl who 'previously could read a chapter out of the Bible, but then developed defective memory, her head drooped forward unto her chest, her legs became weak and unsteady'. Retrospectively, this sounds rather like myxoedematous cerebellar degeneration, a rare complication of hypothyroidism. In 1966 Ramsey gave the first full description of thyrotoxic myopathy[7]. Rheumatic or musculoskeletal conditions comprise over 150 diseases

and syndromes, which are usually progressive and associated with pain (WHO)[8]

Pathogenesis and the characteristics of some of these disorders are explained in terms of autoimmunity and are also referred to as autoimmune disorders. As inflammation is one of the results of this autoimmune response against specific structures of the musculoskeletal system, the term inflammatory arthritis is also used to describe those [9]

Rheumatic disorders: Rheumatic disorders are the chronic systemic autoimmune diseases characterized by a symmetrical inflammation of the synovium, resulting in tenderness and destruction of bone and cartilage in various joints, particularly the smaller parts of the hands and feet.

Prevalence: The mean annual incidence rate of autoimmune hypothyroidism is up to 4 per 1000 women and 1 per 1000 men. The mean age at diagnosis is 60 years, and the prevalence of overt hypothyroidism increases with age. Subclinical hypothyroidism is found in 6–8% of women (10% over the age of 60) and 3% of men. The annual risk of developing clinical hypothyroidism is about 4% when subclinical hypothyroidism is associated with positive thyroid peroxidase (TPO) antibodies[10]. The prevalence of thyroid antibody positivity in the general population is 15% to 25% in women and 5% to 10% in men. Graves' disease is less prevalent than Hashimoto's thyroiditis[11]. The prevalence of thyroid dysfunction and autoimmunity in rheumatoid arthritis according to previous studies were 10-20% (13, 14, 2, and 3) and 15-30% respectively. Subclinical hypothyroidism is defined as mild elevation of serum thyrotropin (TSH) levels and normal circulating thyroid hormone levels. Antithyroid antibodies are positive in 90% of affected patients[12].

Measurement of Thyroid Hormones: TSH is the most reliable and sensitive screening test for thyroid dysfunction as autoantibodies may persist for many years without thyroid dysfunction and allows both hypothyroidism and hyperthyroidism to be diagnosed with certainty. TSH levels change dynamically in response to alterations of T4 and T3, a logical approach to thyroid testing is to first determine whether TSH is suppressed, normal, or elevated. Hypothyroidism: Hypothyroidism is a clinical syndrome caused by decreased levels of thyroid hormones.

Systemic lupus erythematosus: The association between SLE and thyroid dysfunction was first described in 1961 in reports of the association between SLE and HT[13]. In his study has not evidenced greater risk of AITD in patients with SLE, however several other studies like Kumar et al (2010)[14] have shown that association.

Although the pathogenic mechanism has remained unknown, genetic influence has been suggested by[15] in a study of 35 families with several cases of SLE concomitant with AITD, in which a gene of susceptibility was identified in 5q14.3-q15 (major *locus* of susceptibility for SLE, also found in AITD). That locus can be shared by patients with SLE and AITD, evidencing a potential genetic link between both diseases.

Rheumatic polymyalgia and vasculitis: Rheumatic polymyalgia (RPM) and giant cell arteritis (GCA) have been studied since 1971, there is no definite conclusion about their association with HT[16,17] .In prospective studies with 287 and 39 patients, respectively, have reported no association between RPM or GCA and thyroid abnormalities[17].however, studying 367 patients, have reported hypothyroidism in 4.9% of them and despite the statistically significant results, the population

controls of 84 normal participants showed an abnormally low disease rate..

Rheumatic fever: The first references to the association between rheumatic fever and thyroid dysfunction date back to 1961, with the study of 6 women with rheumatic heart valve disease, who evolved with thyroiditis, anti-Tg and hyperthyroidism[18].Studies assessing the association between thyroid dysfunction and rheumatic fever, in which all adults have chronic rheumatic cardiac disease (CRCD), are scarce in the literature.

Material and methods

This observational prospective study was conducted in the patients attending Medicine department at a SAIMS Medical College & Hospital-Indore from November 2019 to November 2021. In rheumatology/medicine outpatient/wards diagnosed patients with rheumatic disorders, after considering exclusion and inclusion criteria, were consecutively included in the study.

Inclusion Criteria: Patients with rheumatic disorders. Patients consenting to be included in the study

Exclusion Criteria: Pregnancy, Children <12 years of age, Patients not consenting to be included in the study.

Results

Fifty six patients of rheumatic disorders were studied for the thyroid function in the department of Medicine at a tertiary hospital over the period of November 2016 to November 2018.

Age: Mean age of 56 patients studied was 43.68 years (Range 23-70 years). Majority patients belonged to the age of 31 to 50 years (67.9%)

Table 1: Age-wise Distribution

	Frequency	Percent
≤ 30	5	8.9
31 - 40	22	39.3
41 - 50	16	28.6
51 - 60	8	14.3
> 60	5	8.9
Total	56	100.0

Sex: Majority patients were female i.e. 47 (83.9%) while males were 9 (16.1%)

Table 2: Sex-wise Distribution

Sex	Frequency	Percent
Female	47	83.9
Male	9	16.1
Total	56	100.0

Table 3: Symptoms reported

Symptoms	Total n=56	
	No.	%
Joint pain	55	98.2
Joint Swelling	46	82.1
Stiffness	33	58.9
Fatigue	24	42.9
Weight gain	9	16.1
Weakness	5	8.9
Backache	4	7.1
Palpitation, Giddiness	2	3.6
Dryness of eyes,		
Fever, skin lesions	1	1.8

Multiple joint pains are the common symptom (98.2%). Fatigue in 24 (42.9%), stiffness (58.9%), swelling of joints in 46(82.1%) and weight gain in 9 (16.1%) was common symptoms. Weakness was reported in 5 (8.9%) patients, while other symptoms are seen in table 5 (Figure 3). Dryness of eyes, mouth and dysphagia was reported in a patient of Sjogren syndrome. Palpitation and giddiness was reported in 2 RA patients out of which 1 were hypertensive.

Table 4: Past History

History	Frequency	Percent
Hypertension	5	8.9
Diabetes Mellitus	5	8.9
Hypothyroidism	7	12.5

Family History: Four patients (7.1%) gave history of joint pain and arthritis in the family. However, no history of thyroid disorder was reported.

Personal History: Ten (17.9%) patients reported decreased appetite. Sleep was adequate. Bowel bladder habits were normal. No major addictions or allergies were reported.

Table 5: Lipid profile

Parameter	Level mg/dL	Frequency	
Cholesterol	≤ 250	53	94.6
	> 250	3	5.4
Triglycerides	≤170	49	87.5
	>170	7	12.5

Similarly, in 3 (5.4%) patients serum cholesterol and in 7 (12.5%) triglyceride levels were above normal limits.

Table 6: Thyroid Status in Relation to Gender

Thyroid Dysfunction	Total No. N=56 (%)	Female n=47	Male n=9
Euthyroid	45 (80.36)	37 (78.72)	8(88.89)
Hypothyroid	11(19.64)	10(21.27)	1(11.11)
Hyperthyroid	0	0	0

Fisher exact test P= 0.671

Out of 11 patients having hypothyroidism, 10 (21.27%) were female and 1(11.11%) was male. This gender proportion is statistically not significant (P= 0.671). Only male patient with hypothyroidism had SLE and diabetes mellitus

Table 7: Age Wise Distribution of Thyroid Dysfunction

Age	Total No. n=56	Euthyroid n =45	Hypothyroid n =10	Subclinical Hypothyroid n =1	Hyperthyroidism n =0
≤ 30	5	5 (100)	0	0	0
31 - 40	22	17 (77.27)	5 (22.73)	0	0
41 - 50	16	12 (75)	3 (18.75)	1 (6.25)	0
51 - 60	8	6 (75)	2 (25)	0	0
> 60	5	5 (100)	0	0	0

Mean age of patients with thyroid disorder was 42.73 years (SD± 7.81) and in euthyroid it was 43.91years (SD± 11.93). Hypothyroidism in rheumatic disorders is common during age of 31-50 years (Fig. 10). Age difference observed in patients with or without thyroid dysfunction is not statistically significant (P= 0.771).

Table 8a: Rheumatological Treatment

Drugs	Euthyroid n=45		Hypothyroid n=11		Z Value	P Value	Mean Joints involved	
	No.	%	No.	%			Euthyroid	Hypothyroid
HCQ + Predni	18	40	1	9.09	1.94	0.026	7.3	4
HCQ	7	15.56	4	36.36	1.56	0.059	7.4	8.65

Predni	6	13.33	1	9.09	0.38	0.352	9.3	4
HCQ + Predni + MTX	6	13.33	3	27.27	1.13	0.129	10.5	9.6
MTX + Predni	3	6.67	0	0	0.88	0.189	8.67	0
HCQ + MTX	2	4.44	2	18.18	1.59	0.056	6.5	11
MTX	1	2.22	0	0	1.01	0.999	6	0
Predni + HCQ+ Sufasalazine	1	2.22	0	0	1.01	0.999	13	0
HCQ + MTX + Sulfasalazine	1	2.22	0	0	1.01	0.999	4	0

HCQ: Hydroxychloroquine, Predni: Prednisolone, MTX: Methotrexate

Table 8b: Antirheumatic Treatment-Drug Category wise

Drugs	Euthyroid n=45	Hypothyroid n=11	p-value	Mean Joints involved	
				Euthyroid	Hypothyroid
1 DMARD	29 (64.4%)	5 (45.5%)	0.248	7.4	7.72
2 DMARD	9 (20.0%)	5 (45.5%)	0.080	9.8	10.16
3 DMARD	1 (2.2%)	0	0.999	4	0
Prednisolone	6 (13.3%)	1 (9.1%)	0.703	9.3	4
Prednisolone with DMARD	28 (62.2%)	4 (36.4%)	0.120	8.34	8.2

As seen in Table 24b, in euthyroid patients one, two and three DMARDs were given in 29 (64.4%), 9 (20.0%) and 1 (2.2%) while in hypothyroid patients in 5 (45.5%), 5 (45.5% and 0 patients, respectively. Two DMARDS were needed more often in hypothyroid patients which is however is not statistically significant (P>0.05). Prednisolone is given either alone or with DMARDs. Patients were tolerating the treatment. In hypothyroid patients requiring 2DMARDs have slightly more joint involvement seen while 13.3% euthyroid patients needed only prednisolone with more joint involvement compared to hypothyroid in 9.1%

Discussion

In this observational study 56 patients of diagnosed rheumatic disorders were studied for the thyroid function in the department of Medicine at a tertiary hospital during the period of November 2019 to November 2021. Rheumatoid arthritis was the commonest rheumatic disorder observed (45 patients 80.3%). SLE was found in 5 (8.9%), Sjogren's syndrome in 2 (3.6%), fibromyalgia 1(1.8%) and multiple connective tissue disorder in 2 (3.6%) and polymyalgia rheumatica 1(1.8%) was found. Out of these 56 patients, 11 (19.64%) had hypothyroidism. Out of these 11 patients, 10 (17.85%) had overt hypothyroidism while 1(1.79%) had subclinical hypothyroidism. No patient had hyperthyroidism. Out of 11 patients with hypothyroidism 10 were females (90.9%). Maximum hypothyroidism was found in RA. i.e. in 9 (20%) patients.

In present study mean age was 43.68 years (Range 23-70 years). Majority patients belonged to the age of 31 to 50 years (67.9%). Majority patients were female i.e. 47 (83.9%) while males were 9 (16.1%). Except one patient all are married. Eight (14.3%) patients were uneducated while 48 (85.7%) were educated.

Majority of the patients were unemployed i.e. 41(73.2%). Out of 47 women 74.47% were menstruating. Rheumatic disorders affect the productive period of life.

Joshi et al (2017)[19]reported the age of 41.4 years in hypothyroid group and 36.9 years in euthyroid group (Table D1). Chandrashekara et al. (2017)[20] reported mean age of 48.98 years in a large Indian study on patients of RA.21 in their study in RA with 70 patients (9 males and 61 females) mean 47 years (range 15–77) was observed. Female: male ratio of all rheumatic disease patients is 5.2:1 in present study. Chandrashekara et al. (2017)[20] reported F: M ratio as 5:1.[22] reported 4-5 times higher prevalence in females with RA at age < 50 years while 2-fold at age of 60-70 years. Inflammatory rheumatic diseases such as RA and SLE show a striking female predominance ranging from 3:1 in RA up to 9:1 in SLE. The background for that gender bias is not fully understood yet, but seems to be the result of a complex interaction between sex hormones, (epi-) genetics, and possibly even the composition of gut microbiota. Among RA patients, women are more likely to acquire conditions like thyroid dysfunctions, fibromyalgia, and depression than their male counterparts[23.]

In present study, out of 56 patients of rheumatic disorders, 11 (19.64%) had hypothyroidism. Out of these 11 patients, 10 (17.85%) had overt hypothyroidism while 1(1.79%) had subclinical hypothyroidism. No patient had hyperthyroidism. Joshi et al (2017)[19] reported 38.46% patients with hypothyroidism in a study from Department of Medicine, Indore in RA. In present study 9 (20%) out of 45 patients of RA had hypothyroidism. These all 9 patients were female[23]. In 75 patients of autoimmune diseases had AITD (16%), RA (4%), SLE (2.6%), and Lambert–Eaton myasthenic syndrome (1.3%). of these 12 (16%) patients of AITD, 5 (41.7%) had hypothyroidism, 4 had hyperthyroidism and 3 were euthyroid.

Anoop et al (2018)[23] In 100 patients of RA from Bangalore found 22% patients had biochemical evidence of thyroid dysfunction while 15 (15%) with hypothyroidism. Present study correlates well with that of Anoop et al..

In present study, all the patients were on antirheumatic treatment alongwith the treatment of concomitant ailments. As seen in Table 24a, 18 euthyroid and 1 hypothyroid patient required two drugs which was significantly different statistically (P=.026). However, in rest of them double or triple drugs were required with adequate clinical response. In present study prednisolone and methotrexate was not required in higher doses in hypothyroid patients than euthyroid patients[24]. Reported hypothyroid patients requiring prednisolone in doses of 5–20 (7.8 ± 9.2) mg/day while euthyroid patients 5–10 (3.2 ± 1.8) mg/day. Methotrexate was required in 12.5 ± 25 (12.7 ± 6.5) mg/week in hypothyroid patients while 10–12.5 (8.5 ± 1.2) mg/week in euthyroid patients of RA. In Colombian study (36) methotrexate was used in 87.57% RA and 96.15% RA with AITD (NS) while in present study in 13 (28.9%) of euthyroid and 5 (45.5%) of hypothyroidism patients which is also not significant (P=0.292).

Rheumatic complaints start simultaneously with the first symptoms of hypothyroidism and joint pain and swelling usually disappear with thyroxine substitution. As thyroxine replacement may reverse the rheumatic

complaints, thyroid function should be performed as part of the biochemical profile in patients

Conclusion

Fifty six patients of rheumatic disorders were studied for the thyroid function in the department of Medicine at a tertiary hospital over the period of November 2019 to November 2021. Mean age of 56 patients studied was 43.68 years (Range 23-70 years). Majority patients belonged to the age of 31 to 50 years (67.9%). Proportion of thyroid dysfunction in rheumatic disorders is 19.64 %. Rheumatoid arthritis (80.3%) and SLE (8.9%) are common rheumatic disorders and occur mainly in females (83.9%). Abnormal thyroid function is mainly in the form of both overt and subclinical hypothyroidism. Higher proportion of hypothyroid patients requires one or more DMARDs for adequate clinical response; however it was not statistically significant. In view of high proportion of thyroid disorders in patients of rheumatic disorders, regular thyroid function study in addition to the search for co-morbidities in these patients to treat successfully with thyroxine treatment will help improve clinical outcome.

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