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EVALUATION OF THYROID FUNCTION ABNORMALITIES IN PATIENTS HAVING CONNECTIVE TISSUE DISORDERS (CTD) ATTENDING A TERTIARY CARE CENTRE IN KOLKATA

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ABSTRACT

Background: Although thyroid disease is common in the general population, there appears to be an increased frequency of thyroid dysfunctions in association with many autoimmune rheumatic diseases. The associations of thyroid dysfunctions and connective tissue diseases and the presence of anti Thyroid Peroxidase antibodies(TPO) in patients with thyroid diseases are reviewed here. **Objective:** Aim of this study was to study prevalence of thyroid autoimmunity and type of any thyroid hormonal dysfunction in patients with Connective Tissue Disorders both treatment-naive and on treatment, in comparison to age- and sex-matched healthy controls. **Method:** In this single center, cross-sectional study in the year 2017-2018, *35* patients with connective tissue disorders and 35 age and sex matched healthy controls were selected. Thyroid profile as well as thyroid antibody of both groups (CTD and healthy control) was investigated and compared. **Results:** Out of 35 CTD patients 37.14% (vs 22.85% in control) had thyroid dysfunction. Clinical hypothyroidism was the commonest dysfunction, observed in 25.71% (vs 8.5% in control) of CTD patients. Subclinical hypothyroidism (only TSH raised) was seen in only 8.5% (vs 14.28% in control). Hyperthyroidism was seen in one patient (Overlap group). Presence of Anti TPO Antibody was statistically significant in CTD group when compared with healthy group(p-0.002). SLE patients had a significantly higher rate of thyroid diseases and anti TPO positivity than matched controls (p-0.048 and 0.002). **Conclusion**: In conclusion, CTD patients frequently have abnormal results of one or more of thyroid function tests. All CTD patients should be thoroughly evaluated for presence of thyroid dysfunction as well as anti TPO antibody.

KEYWORDS: CTD, Thyroid dysfunctions, TPO.

INTRODUCTION

Connective tissue disorders refer to a group of disorders involving the protein-rich tissue that supports organs and other parts of the body. Examples of connective tissue are fat, bone, and cartilage. These disorders often involve the joints, muscles, and skin, but they can also involve other organs and organ systems, including the eyes, heart, lungs, kidneys, gastrointestinal tract, and blood vessels.

Connective tissue disorders include a family of more than 200 different disorders that affect connective tissue. Connective tissue disorders are caused primarily by gene mutations affecting the production of tissue and by a number of different specific and overlapping autoimmune diseases.

In autoimmune connective tissue disorders, specific organs or multiple organs may be affected. Until the late 70's, most systemic or rheumatological autoimmune disease were referred to as connective tissue diseases. But now connective tissue diseases are classified as either.

1.autoimmune connective tissue disorders such as lupus disorder, rheumatoid arthritis, systemic sclerosis, polymyositis, dermatomyositis, mixed connective tissue disease and Sjogren's syndrome or.

2.heritable connective tissue disorders such as Ehlers-Danlos syndrome, epidermolysis bullosa, and Marfan syndrome caused by gene mutation.

AIMS AND OBJECTIVES

1. To study prevalence of thyroid autoimmunity in patients with Connective Tissue Disorders, both treatment-naive and on treatment, in comparison to age- and sex-matched healthy controls.
2. To study prevalence and type of any thyroid hormonal dysfunction in Connective Tissue Disorders.

MATERIALS AND METHODS

- ***Study Areas:*** Opd And Ipd Of School Of Tropical Medicine, Kolkata.
- ***Study Population:*** Patients Aged More Than 15years With Connective Tissue Disorders Who Are Attending Opd And Are Admitted (Ipd) At School Of Tropical Medicine.
- ***Study Period:*** July 2017- June 2018.
- ***Sample Size:*** 70 (35 With Ctd +35 Healthy Controls).

Sample Design Selection of The Patient: *35* patients with connective tissue disorders and 35 age and sex matched healthy controls was selected. Attempt was made to select minimum 4 persons(2 males and 2 females each) in the healthy group between age bands of 15-25 years, 26-35 years, 36-45 years and above 45 years. The thyroid profile as well as thyroid antibody of both groups(patients with CTD and healthy) was investigated and compared. These groups were screened and finally recruited for the study using following inclusion and exclusion criteria.

Inclusion Criteria

- Patients with diagnosed connective tissue disorder in the age group more than 15 years.

Exclusion criteria

- Patients having connective tissue disorder already being diagnosed with thyroid function abnormality and taking appropriate medications.
- Any type of Malignancy with connective tissue disease
- HIV infected patients with connective tissue disease.
- Patients known to take drugs affecting thyroid function like iodine, lithium, amiodarone, phenytoin, interferon etc.

- **Study Design- Cross Sectional Observational Study**
- **Parameters Studied.**
- Detailed history.
- Physical examinations.
- Routine lab investigation: (a) complete haemogram (b) Liver function tests (c) urea, creatinine (d) fasting blood sugar(e) lipid profile (f) sodium,potassium (g) T3, T4, TSH (h) HIV-1 and 2 antibody (i)chest X-ray, (j) USG whole abdomen, (k) ECG (l)special investigation like Anti TPO antibody ,(m) USG Thyroid gland if any localised or generalised thyroid swelling is observed clinically, (n) FNAC of thyroid nodule as and when required.

- **Study Tools**
  - Pre-designed and pre-tested schedule for data collection.
  - Prescription used by the patient.
  - Other allied instruments required during physical examination of the patients.

Study Techniques

- Patients with diagnosed connective tissue disease are further evaluated for any thyroid function abnormalities and also considering their inclusion and exclusion criteria's.
- Interviewing the patient for proper medical history.
- Clinical examination.
- Scrutiny of biochemical, radiological, micro-biological reports.

Plan for Analysis Of Data*:* The data was analysed using appropriate statistical techniques.

Ethics

The study protocol was submitted to the clinical Research Ethics Committee of Calcutta School of Tropical Medicine, Kolkata for ethics review and approval. The study commenced only after the ethics approval was duly obtained.

RESULTS AND ANALYSIS

35 patients of connective tissue disorder and 35 age and sex matched healthy individuals were studied. We examined the prevalence of thyroid dysfunction and the production of anti-thyroid antibodies (anti TPO) in patients with connective tissue disorders and association between antibody production and disease activity.

Both these groups were studied and analyzed according to their age, sex, hematological profile, liver function test, kidney function test, thyroid profile and thyroid autoantibody production.

Age Distribution of Patients

Among these 35 CTD patients, 15 patients were from age group 35-44 years of age, 7 each were from 15-24 and 25-34 years of age, rest were above 45 years of age.

Age	No. of patients
15-24	7
25-34	7
35-44	15
45-54	2
55-64	4
Grand Total	**35**

Figure 1: Table showing age distribution of patients.

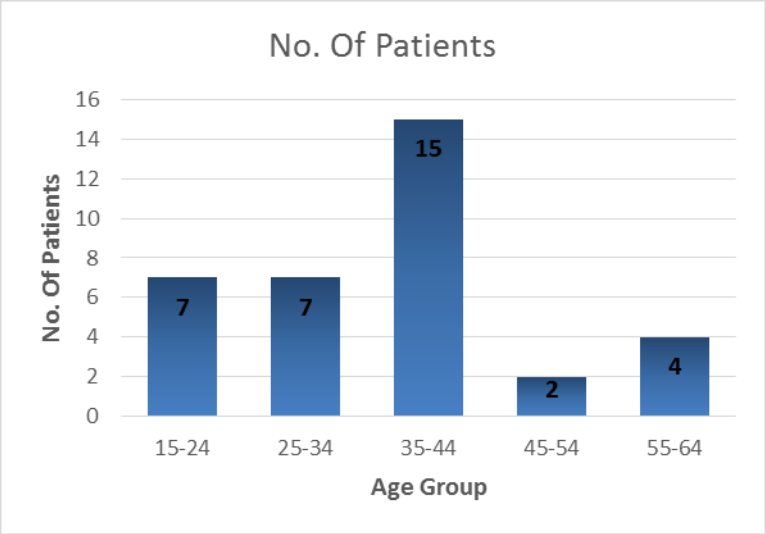

Figure 2: Bar diagram showing number of patients according to age group.

Sex distribution of patients
Majority were females.

Figure 3: Table showing sex distribution of patients.

Row Labels	Count of value
F	33
M	2
Grand Total	**35**

Signs and Symptoms
According to clinical signs and symptoms, out of 35 connective tissue disorder patients, 13 patients had malar rash(37%), 8 had oral ulcer(22%), 6 had photosensitive skin rash. 2 patients had skin tightening. 11 patients gave history of hair loss. Dryness of mouth was present in one of them. 20 patients had polyarthralgia(57%). 1 patient had severe myalgia.

Haematological profile of patients
15 patients had mild anaemia(10-12 gm/dl), 12 had moderate anaemia(8-10mg/dl), 3 had leucopenia (<4500/µL)-lowest being 2500/µL and 6 of them had thrombocytopenia(<150000/µL)-lowest being 100000/µL. The type of anaemia in all these patients was normocytic normochromic.

Mild anaemia	Moderate anaemia	Severe anaemia	leucopenia	Thrombocytopenia
15	12	---	3	6

Figure 4: table showing haematological profile of connective tissue disorder patients.

Metabolic alterations
Among 35 connective tissue disorder patients, none were diabetic. Only a small number of patients had altered lipid profile. 4 patients out of 35 were having high levels of triglyceride(maximum value was 350mg/dl).

Other biochemical parameters
3 patients had hyperglobulinemia.(maximum value was 4.8gm/dl)
Creatinine levels were normal among all these patients.(cut off value for female was 1.1 mg/dl and for male was 1.3mg/dl).

Liver enzymes were normal except in one patient who had very high SGOT and SGPT. He also complained of severe myalgia. CPK was also very high. Skin biopsy was suggestive of dermatomyositis. Hepatitis viral markers were negative.

He finally expired before we could start the definitive treatment.

Thyroid dysfunction in study group
Out of 35 connective tissue disorder patients, 13 patients(37.14%) had thyroid dysfunction. Clinical hypothyroidism was the commonest dysfunction, observed in 25.71% of patients, who belonged to an older age group. Subclinical hypothyroidism (TSH alone raised) was the next dysfunction seen in 8.5% of patients (mean age 28years). Hyperthyroidism, occurred in only one of them.

Among 12 patients of hypothyroidism, 7 gave history of fatigue and weakness. 5 had history of weight gain. 3 of them complained of depressed mood. There was no significant history of dry skin among them.

Clinically, no patient had goiter.

On examination, none showed delayed relaxation of ankle jerk. Pericardial effusion was not documented in any patient. Anti thyroid peroxidase antibody (anti TPO) was positive in all these hypothyroid patients.

The hyperthyroid patient complained of palpitation and insomnia.

Diagnosis of CTD in study group

Among 35 CTD patients, 25 patients were diagnosed as SLE based on their clinical and serological profile as per ACR criteria. 4 had overlap syndrome, 3 systemic sclerosis, 2 MCTD and 1 Sjogren's syndrome.

CTD	No of patients
Sjogren's	1
MCTD	2
Overlap	4
Systemic Sclerosis	3
SLE	25
Grand Total	**35**

Figure 5: Table showing distribution of patients among different types of connective tissue disorders(CTD).

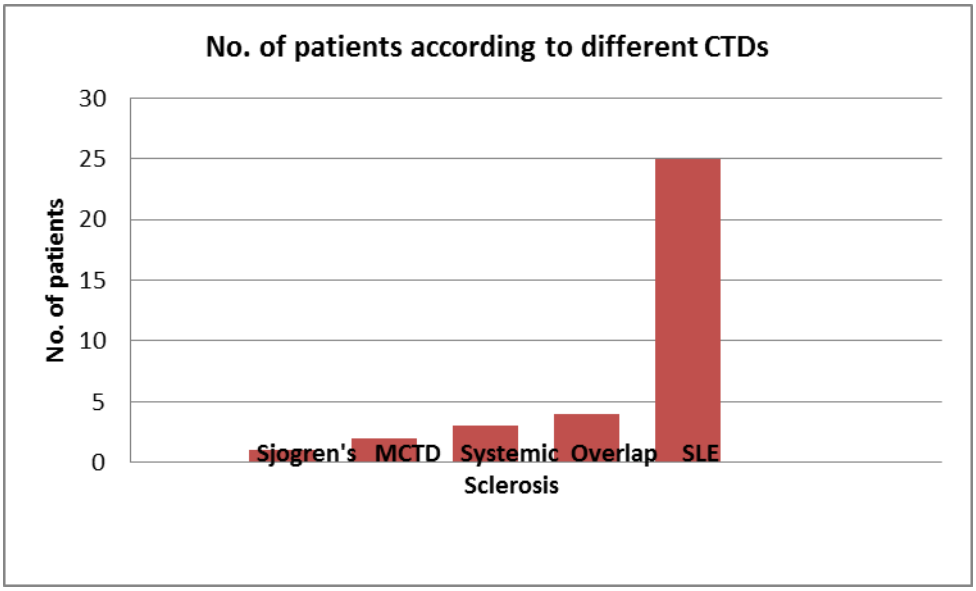

Figure 6: Bar diagram showing distribution of patients among different types of connective tissue disorders(CTD).

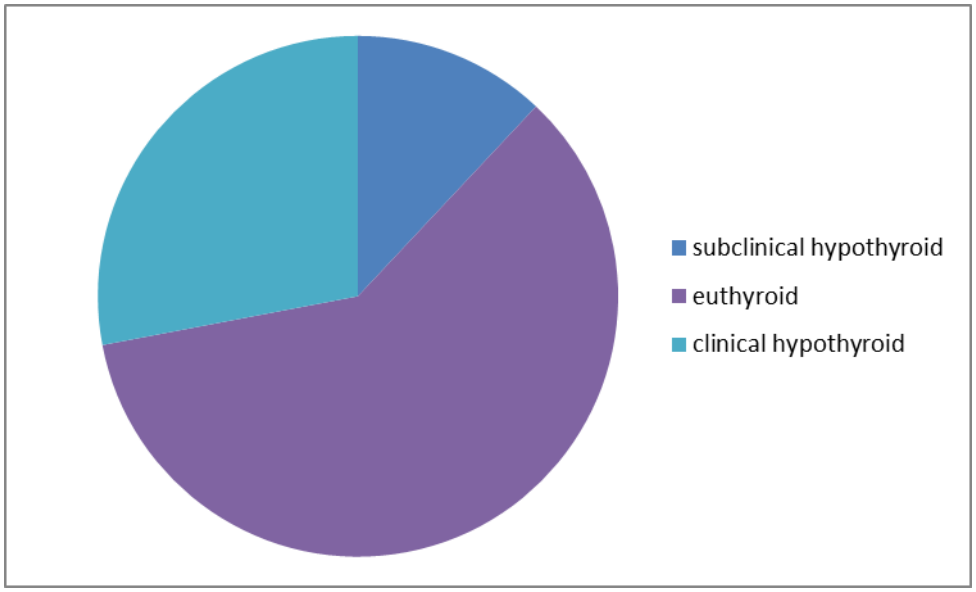

Figure 7: Pie chart showing thyroid disorders in SLE patients.

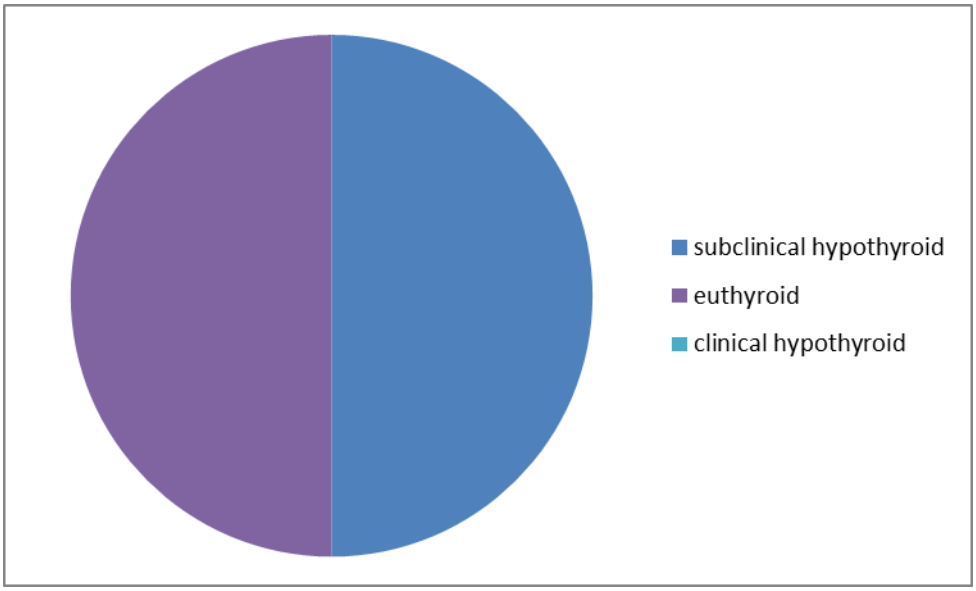

Figure 8: Pie chart showing thyroid disorders in MCTD patients.

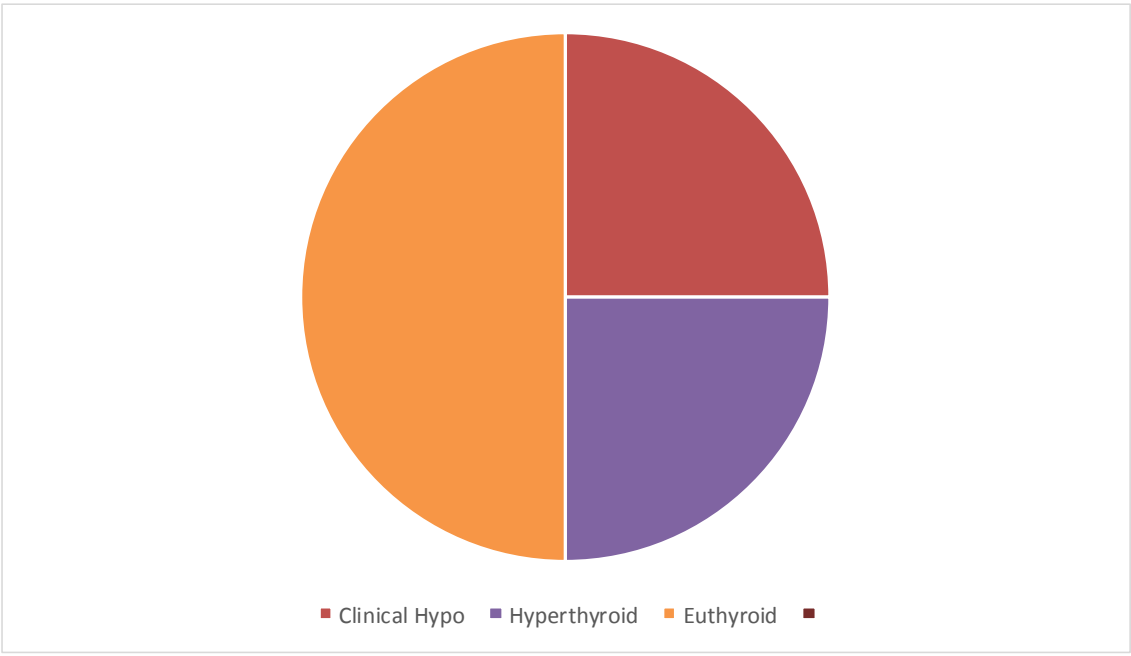

Figure 9: Pie chart showing thyroid disorders in Overlap syndrome.

Control group-Age distribution.

Age group	No of patients
15-25	2
26-35	10
36-45	5
>45	18

Majority were above 45 years of age.

Sex distribution

Sex	No of patients
Male	5
Female	30

5 of them had history of fatigue and weakness.

Among 35 healthy controls, there was no significant change in hematological profile nor in the liver function tests.

Thyroid abnormalities in control group

Among 35 healthy controls, 8 were having thyroid function abnormalities. (22.85%) Out of these 35 healthy controls, 5 were having subclinical hypothyroidism (14.28%), and 3 were having clinical hypothyroidism(8.5%).

Figure 10: Table showing thyroid function abnormalities in healthy controls.

Age	Subclinical hypothyroid	Euthyroid	Clinical Hypothyroid	Total patients
15-25	0	1	0	1
26-35	2	8	1	10
36-45	1	4	0	5
Above 45	2	14	2	19
Total	5	27	3	35

Anti TPO was positive only in 2 of these patients (5.71%).

Comparison of presence of anti TPO in study and control group.

	CTD	Control	Marginal row totals
Anti TPO positive	12 (7) [3.57]	2 (7) [3.57]	14
Anti TPO negative	23 (28) [0.89]	33 (28) [0.89]	56
Marginal column totals	35	35	70

The chi-square statistic is 8.9286. **The p-value is 0.002807.** This result is significant at p< 0.05.

Comparison of clinical hypothyroidism in SLE VS control group

	SLE	Control	Marginal row totals
Clinical hypothyroid	7 (4.33) [1.23]	3 (5.77) [1.33]	10
Euthyroid	15 (17.77) [0.43]	27 (24.23) [0.32]	42
Marginal column totals	22	30	

The chi-square statistic is 3.8899. The p-value **is 0.048578. This result is significant at p<0.05.**

Comparison of presence of anti TPO in SLE vs. control group.

	SLE	Control	Marginal row totals
Anti TPO positive	9 (4.58) [4.26]	2 (6.42) [3.04]	11
Anti TPO negative	16 (20.42) [0.96]	33 (28.58) [0.68]	49
Marginal column totals	**25**	**35**	**60**

The chi-square statistic is 8.934. The p-value is **0.002799. The result is significant at p<0.05.**

DISCUSSION

1.SLE

Table showing prevalence of thyroid disorders and anti-TPO positivity in different studies

	Kumar K et al.	Porkodi et al.	Present study
Subclinical hypothyroid	12%	20%	8.57%
Clinical hypothyroid	14%	60%	20%
Hyperthyroid	2%	10%	---
Anti TPO positivity	18%	10%	25.71%

In the study by Kumar K et al[2] from Kolkata, hundred SLE patients as well as 100 age and sex matched healthy controls were studied. Thirty-six (36%) lupus patients had thyroid dysfunction when compared to 8 (8%) of controls and all of them were women. Primary hypothyroidism was the commonest dysfunction in 14 (14%), while subclinical hypothyroidism and subclinical hyperthyroidism was seen in 12 (12%) and 2 (2%), respectively. 18% patients had anti TPO positive.

In another study by Porkodi[1] et al, 20 out of 153 SLE patients (13.1%) had thyroid dysfunction. All were females. Hyperthyroidism, a less common abnormality (10%) occurred in younger individuals (mean age 27 years). Subclinical hypothyroidism (TSH alone raised) was the next dysfunction seen in 20% of patients (mean age 28 years). Clinical hypothyroid was the commonest dysfunction in 60% of patients, who belonged to an older age group (mean age 30.4 years). 10% patients had anti TPO positive.

In the present study, out of 25 SLE patients in study group, 10 (40%) patients had thyroid dysfunction. All were female. Among SLE patients, subclinical hypothyroidism was seen in 12% of patient and clinical hypothyroidism was seen in 28% of patients. Anti TPO antibody was positive in 25.71% patients.

Overlap syndrome

According to the study by Lin WY et al[12] from China, the cumulative incidence of thyroid disease in SLE patients was lower than in controls (8.1% vs. 16.9%, p < 0.001). Among SLE patients, 39.7% had **overlap syndrome**. The overlap syndrome group had a higher

cumulative incidence of **thyroid diseases (10.96%** vs. 4.57%, p < 0.0001**), hypothyroidism (3.86%** vs. 1.93%, p = 0.017), and **autoimmune thyroiditis (4.63%** vs. 0.71%, p < 0.0001) than SLE patients without overlap syndrome. Comparing the data with the non-SLE-matched control group by logistic regression model revealed a decreased risk of thyroid diseases with odds ratios (ORs) of 0.25 and 0.62 [95% CI 0.18-0.33, 0.48-0.80], and hyperthyroidism with ORs of 0.21 and 0.30 (95% CI 0.14-0.31, 0.20-0.45) in SLE patients without and with overlap syndrome.

SLE patients without overlap syndrome had a lower risk of hypothyroidism with an OR of 0.53 (95% CI 0.53-0.86) and autoimmune thyroiditis with an OR of 0.26 (95% CI 0.12-0.56). SLE patients with overlap syndrome showed a similar risk of hypothyroidism with an OR of 0.92 (95% CI 0.66-1.53) and a higher risk of autoimmune thyroiditis with OR of 1.69 (95% CI 1.14-2.51).

In the present study, 4 were having overlap syndromes. Of these four patients, 1 was clinically hypothyroid (25%), 1 was hyperthyroid(25%), rest were euthyroid (50%).Anti TPO was positive in two of these four patients.(50%).

MCTD

2 patients were having Mixed Connective Tissue Disorder. One was diagnosed to be clinically hypothyroid. She had anti TPO positive.

Systemic Sclerosis

3 patients were diagnosed as systemic sclerosis. None of them had any thyroid dysfunction.

Sjogren's syndrome

1 was having Sjogren's syndrome without any thyroid function abnormalities.

In the study by Lazarus and Isenberg (41), 16% of the SS patients developed AITD. The most common clinical manifestation of AITD in SS was hypothyroidism, even though subclinical AITD was probably more common.

In the vast majority of the cases, hypothyroidism had been diagnosed before the diagnosis of SS.

In the study by Hansen et al, 36% had anti TPO positive. 18% developed hyperthyroidism.

High prevalence of autoimmune thyroid disease and thyroid dysfunction(in almost 1/3rd) is found in primary Sjögren's syndrome (pSS). In a Frenchstudy[27] of 137 biopsy proven pSS, with 6 years follow up, 30% of pSS patients had thyroid dysfunction and11% had anti-TPO and 3% and anti-Tg antibodies.

The most common thyroid disorder found was autoimmune thyroiditis and the most common hormonal pattern was sub-clinical hypothyroidism.[5]

Caramaschi et al[7]from Italy evaluated the co-occurence of Hashimoto thyroiditis in primary Sjogren's syndrome. In their study, which included 100 patients, they observed that Hashimoto thyroiditis was associated with primary Sjogren's syndrome in 27 cases.

Since our study was for one year duration we didn't have enough number of patients to make any significant observation regarding this.

SUMMARY AND CONCLUSION

Present study group had 25 SLE patients, 4 overlap syndrome, 3 systemic sclerosis, 2 MCTD and 1 Sjogren's syndrome.

Out of 25 SLE patients, 3 had subclinical hypothyroidism, 7 had clinical hypothyroidism. Rest were euthyroid.

Out of 4 overlap syndrome, 1 had clinical hypothyroidism.

Out of 2 MCTD patients, 1 had clinical hypothyroidism.

No thyroid function abnormalities were detected in systemic sclerosis and Sjogren's syndrome.

None of the patients had thyroid gland enlargement.

Among 10 hypothyroid patients of SLE subgroup, 9 had anti TPO positive.

Out of 2 MCTD patients, 1 had anti TPO positive.

2 patient of Overlap syndrome had anti TPO positive.

There was significant association between thyroid autoantibody and connective tissue disorder compared to control group.

SLE patients had a significantly higher rate of thyroid diseases and anti TPO positivity than matched controls.

However, there was no correlation between thyroid autoantibody presence and disease activity or functional impairment.

Findings of the study suggest that all connective tissue disorder patients should be thoroughly evaluated for presence of thyroid dysfunction as well as anti TPO antibody.

REFERENCE

1. Porkodi R., Ramesh S., Mahesh A., Kanakarani P., Rukmangathrajan S., Rajendran Panchapakesa C., Thyroid dysfunction in Systemic Lupus Erythematosus and Rheumatoid Arthritis, J Indian Rheumatol Assoc, 2004; 12: 0-0.
2. Kumar K, Kole AK, Karmakar PS, Ghosh A, The spectrum of thyroid disorders in systemic lupus erythematosus, Rheumatol lnt, 2012 Jan; 32(1): 73-8.
3. Danieli, M., Rossetti, L., Fraticelli, P. et al., Autoimmune Thyroid diseases in patients with Undifferentiated Connective Tissue Disease, Clinical Rheumatology, 2000; 19: 42-46.
4. Biro, E., Szekanecz, Z., Danko, K. et al. Association of systemic and thyroid autoimmune diseases, Clinical Rheumatology, 2006; 25: 240.
5. Jara L.J., Navarro C., Brito-Zerón, M.P. et al.,Thyroid disease in Sjogren's syndrome, Clinical Rheumatology, 2007; 26: 1601-1606.

6. Acay A, Ulu MS, Ahsen A, Eroglu S, Ozuguz U, Yuksel S, Acarturk G ,Department of Internal Medicine, Afyon Kocatepe University Faculty of Medicine, Endocr Metab Immune Disord Drug Targets, 2014; 14(3): 182-6.
7. Caramaschi P, Biasi D, Caimmi C, Scambi C, Pieropan S, Barausse G, Adami S. The co-occurrence of Hashimoto thyroiditis in primary Sjogren's syndrome defines a subset of patients with milder clinical phenotype.Rheumatol Int, 2013 May; 33(5): 1271-5. doi: 10.1007/s00296-012-2570-6. Epub 2012 Nov 5.
8. Antonelli A, Fallahi P, Mosca M, Ferrari SM, Ruffilli I, Corti A, Panicucci E, Neri R, Bombardieri S. Prevalence of thyroid dysfunctions in systemic lupus erythematosus Metabolism, 2010 Jun; 59(6): 896-900. doi: 10.1016/j.metabol.2009.10.010. Epub 2009 Dec 16.
9. Unsal E, Oren O, Salar K, Makay B, Abaci A, Ozhan B, Böber E. Turk J The frequency of autoimmune thyroid disorders in juvenile idiopathic arthritis Pediatr, 2008 Sep-Oct; 50(5): 462-5.
10. Atzeni F, Doria A, Ghirardello A, Turiel M, Batticciotto A, Carrabba M, Sarzi-Puttini P. Anti-thyroid antibodies and thyroid dysfunction in rheumatoid arthritis: prevalence and clinical value. Journal of Autoimmunity, 2008 Feb; 41(1): 111-5.
11. Mader R, Mishail S, Adawi M, Lavi I, Luboshitzky R. Thyroid dysfunction in patients with systemic lupus erythematosus (SLE): relation to disease activity. Clinical Rheumatology, 2007 Nov; 26(11): 1891-4.
12. Lin WY[1], Chang CL[2], Fu LS[3], Lin CH[4], Lin HK[1]. Systemic lupus erythematosus and thyroid disease: A 10-year study. J Microbiol Immunol Infect, 2015 Dec; 48(6): 676-83. doi: 10.1016/j.jmii.2014.03.004. Epub 2014 May 26.
13. Posselt RT[1], Coelho VN[1], Pigozzo DC[2], Guerrer MI[2], Fagundes MDC[2], Nisihara R[3], Skare TL[4]. Prevalence of thyroid autoantibodies in patients with systematic autoimmune rheumatic diseases. Cross-sectional study. Sao Paulo Med J, 2017 Nov-Dec; 135(6): 535-540. doi: 10.1590/1516-3180.2017.0089110617.
14. Watad A[1,2], Cohen AD[3,4], Comaneshter D[3], Tekes-Manova D[5], Amital H[1,2]. Hyperthyroidism association with SLE, lessons from real-life data--A case-control study. Autoimmunity, 2016; 49(1): 17-20. doi: 10.3109/08916934.2015.1090985. Epub 2015 Oct 14.
15. Innocencio RM[1], Romaldini JH, Ward LS. Thyroid autoantibodies in autoimmune diseases. Medicina (B Aires), 2004; 64(3): 227-30.
16. Vanderpump MJ, Tunbridge WMG. The epidemiology of thyroid disease. In: The Thyroid: A Fundamental and Clinical Text, 7th ed, Braverman LE, Utiger RD (Eds), Lippincott-Raven, Philadelphia, 1996; 474.
17. Roitt IM, Doniach D, Campbell PN *et al*: Auto antibodies in Hashimoto's disease (lymphadenoid goiter); preliminary communications. Lancet, 1956; ii: 820-821.
18. White RC, Bass BH, Williams E. Lymphadenoid goiter and the syndrome of systemic lupus erythematosus. Lancet, 1961; i: 368-373.
19. Hijmans W, Doniach D, Roitt M *et al*. Serological overlap between lupus erythematosus, rheumatoid arthritis and thyroid autoimmune disease Br. Med J, 1961; 5257: 909-914.
20. Tsai RT, Chang TC, Wang CR, Chuang CY. Chen CY, Thyroid disorders in Chinese patients with Systemic lupus erythematosus Rheumatol Int. 1993, 13: 9-13.
21. Shiroky JB, Cohen M, Ballachey ML, Neville C. Thyroid dysfunction in rheumatoid arthritis; a controlled prospective survey. Ann Rheum Dis, 1993, 52: 454-6.
22. Turnbridge WM, Evered DC, Hall R et al. The spectrum of thyroid disease in community. The Wickham survey. Clin Endocrinol, 1977; 7: 41-93
23. A.T.Y Chan, Z Al Saffar, RC. Bucknall. Thyroid disease in systemic lupus erythematosus and rheumatoid arthritis. Rheumatology, 2001; 40: 353-354.
24. Antonelli A, Fallahi P, Mosca M, Ferrari SM, Ruffi lli I, Corti A et al. Prevalence of thyroid dysfunctions in systemic lupus erythematosus. Metabolism, 2010; 59: 896–900.
25. Pyne D, Isenberg DA. Autoimmune thyroid disease in systemic lupus erythematosus. Ann Rheum Dis, 2002; 61: 70.
26. Rudrajit Paul, Pradip Raychaudhuri, Pradip Kumar Sinha, Sekhar Mookerjee, Kaushik Pandit, Gouranga Santra. Prevalence of systemic lupus erythematosus among patients of hypothyroidism in a tertiary care center. Indian J Endocrinology and Metabolism, 2012; 16: 569-574.
27. Fre´de´rique d'arbonneau, Se´verine ansart, Rozenn le berre, Maryvonne dueymes, Pierre youinou, and Yvonlouis pennec, Thyroid Dysfunction in Primary Sjo¨ gren's Syndrome: A Long-Term Followup Study, Arthritis & Rheumatism (Arthritis Care & Research), 2003; 49:804–809.