

Thyroid Disorders and Autoantibodies in Systemic Lupus Erythematosus and Rheumatoid Arthritis Patients

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To determine the patterns of thyroid dysfunction and autoantibodies associated with SLE and RA patients, twenty patients with SLE and another group of twenty with RA were studied. The results were compared with those of twenty apparently healthy age- and sex- matched controls. All patients were subjected to complete history taking, thorough clinical examination and joint examination. All patients and controls were subjected to the following investigations: T₃, T₄, TSH, antithyroglobulin antibodies (ATGAb) and thyroid peroxidase antibodies (TPOAb). Also, complete blood picture, ESR, RF, ANA, CRP and LE cells were done. This study revealed that thyroid disorders were significantly increased in SLE patients (50%) when compared to RA (15%) ($P < 0.05$). In SLE group, 20% had euthyroid sick syndrome, 20% had hypothyroidism (10% subclinical and 10% biochemical), and 10% had hyperthyroidism (5% subclinical and 5% biochemical). However, in RA, 10% had hypothyroidism (subclinical) and 5% had subclinical hyperthyroidism. TPOAb was found in 15% of SLE and 5% of RA patients and 10% of controls, but the titres were higher in SLE and RA patients. Also, ATGAb was found in 5% of SLE, 30% of RA patients and 10% of controls, but the titres were higher in SLE and RA patients. It is concluded that thyroid abnormalities are more implicated with euthyroid sick syndrome and hypothyroidism (subclinical and overt) than hyperthyroidism in SLE patients. SLE and RA were associated with antithyroid antibodies (TPOAb in SLE and ATGAb in RA). Performance of thyroid function tests in patients with SLE, in particular and RA as a part of the biochemical and immunological profiles, may help in early detection of associated thyroid disorders.

Autoimmune diseases are clearly associated with many factors, such as genetic, hormonal, and environmental factors as well as immune defects (Park et al., 1995). These factors, referred to as the mosaic of autoimmunity, can interact in numerous combinations that may explain the diversity of autoimmune diseases and the association of these diseases in the same patients (Weiss and Shoenfeld, 1991).

Autoimmune thyroid disease, marked by the presence of antibodies directed against thyroid antigen, has been associated with a number of non-organ-specific rheumatological disorders (Pyne and Isenberg, 2002). These associations include systemic lupus erythematosus (SLE) (Boey et al., 1993; Tsai et al., 1993; Pyne and Isenberg, 2002), rheumatoid arthritis (RA) (Caron et al., 1992; Chan et al., 2001), Sjogren's syndrome (Perez

et al., 1995), scleroderma and vasculitides (Gordon et al., 1981; Wiseman et al., 1989).

A number of studies have suggested that thyroid disease is more common in SLE than in general population, but there is disagreement as to whether both hypothyroidism and hyperthyroidism are more common (Goh and Wang, 1986; Tasi et al., 1994; Pyne and Isenberg, 2002), or whether this finding is restricted to hypothyroidism alone (Miller et al., 1993).

Thyroid autoantibodies are a secondary response to thyroid injury; together these antibody tests increase the diagnostic sensitivity of autoimmune thyroid disease and possibly other diseases as well (Inukai and Takemura, 1999). TPOAb are antibodies against thyroid peroxidase enzyme, which catalyzes the iodination of tyrosine and the subsequent biosynthesis of T₃ and T₄. ATGAb

are antibodies against thyroglobulin which is produced by the thyroid cells and stored in the thyroid colloid. High titres of TPOAb or ATGAb are found in Hashimoto's disease and in many patients with Graves disease (Williams, 1998). Moreover, both ATGAb and TPOAb have been found with greater frequency in SLE than in general population, even in SLE patients who do not have clinical thyroid disease (Miller et al., 1993).

The incidence of autoimmune thyroiditis in patients with RA is variable. Hypothyroidism (subclinical and biochemical) was the most frequent thyroid disease associated with RA (Caron et al., 1992; Al Awadhi et al., 1999; Del Puente et al., 2003). RA occurs with high incidence in association with positive antithyroid antibodies (MasukoHongo and Kato, 1999; Del Puente et al., 2003).

The current study was planned to study the thyroid disorders in patients with SLE and RA.

Subjects and Methods

This study included 20 patients with RA and 20 patients with SLE admitted to the Internal Medicine Department of Assiut University Hospital. They fulfilled the American Rheumatism Association criteria of RA (1987) and SLE (1982).

Patient's mean of ages \pm SE were 44.4 ± 1.5 years for RA and 25.8 ± 1.6 years for SLE. Fifteen RA patients (75%) and 17 SLE patients (85%) were females. Twenty age- and sex- matched healthy subjects served as controls. Neither patients nor controls were on corticosteroid therapy. Written consents were taken from patients and controls prior to inclusion into the study. All patients were subjected to complete history taking and thorough clinical examination.

We focused on examination of articular system (morning stiffness, Ritchie articular index (1968), active joints and deformity. Also, we examined all patients for manifestations of hypothyroidism or hyperthyroidism and the presence or absence of goitre.

All patients and controls were subjected to the following investigations:

1. Complete blood picture using cell Dyne 3500.
2. Erythrocyte sedimentation rate (ESR) using Westergreen method.
3. C-reactive protein (CRP) measured by Humatex latex agglutination slide for the qualitative and semiquantitative determination of CRP.
4. Rheumatoid factor (RF) measured by using Stanbio RA factor latex agglutination slide for the qualitative and semiquantitative determination of RF in serum.
5. Lupus erythematosus cell (LE cell) by using Stanbio RAPET SLE latex agglutination slide test for the quantitative determination of anti-dexoxyribonucleic protein (DNP) associated with SLE in human serum.
6. Antinuclear antibodies (ANA) done by ANAFIUDR test which is an indirect fluorescent antibody test. The kit is supplied by Diasorin, Minnesota, USA.
7. T₃, T₄ and TSH using Immulite analyzer kits from Diagnostic Products Corporation, CA, USA.
8. Antithyroglobulin antibodies (ATGAb) using an indirect solid phase enzyme immunometric assay (ELISA) kit from Organteck.
9. Thyroid peroxidase antibodies (TPOAb) using Immulite analyzer, kit supplied by Diagnostic Products Corporation, CA, USA.

Statistical analysis

All data were presented as mean \pm SE or percentages. Comparisons between variables were done by student's t-test and chi square. Relationship between variables were evaluated by Pearson correlation coefficient.

Results

Table 1 represents the clinical data of SLE and RA patients. The duration of illness was 2.9 ± 0.3 months for SLE and 20 ± 2.3 months for RA. Arthritis was found in 50% of SLE patients and kidney affection in 45%. Duration of morning stiffness was 60.2 ± 24 minutes in RA and Ritchie index was 15 ± 5 .

Table 1. Clinical data of SLE and RA patients presented as mean±SE or as percentages.

Variables	SLE patients (n=20)	RA patients (n=20)
Age (years)	25.8±1.6	44.4±1.5
Gender (females/males)	17/3 (85% / 15%)	15/5 (75% / 25%)
Duration (months)	2.9±0.3	20±2.3
Arthritis	10 (50%)	----
Renal affection	9 (45%)	----
Morning stiffness (minutes)	----	60.2±24
Ritchie index	----	15±5

Table 2 shows the peripheral hemogram; ESR, CRP, RF and ANA in SLE, RA and control groups. The mean values of Hb and RBCs were significantly low in SLE versus controls ($P<0.001$ for both). The mean values of platelets was significantly high in RA versus SLE ($P<0.05$). The mean of ESR₁, ESR₂ and the percentage of CRP were significantly high in SLE and RA versus

controls ($P<0.001$ for all). The percentage of ANA was significantly higher in SLE than RA and controls ($P<0.05$ and <0.001 , respectively). Also, the percentage of RF was higher in RA than in controls ($P<0.001$). The percentages of positive LE cells and positive albumin in urine were higher in SLE than in controls ($P<0.001$ and <0.05 , respectively).

Table 2. Peripheral hemogram, ESR, CRP, RF and ANA in SLE, RA and control groups expressed as mean±SE or as percentages.

Parameters	Groups			P value		
	SLE (n=20)	RA (n=20)	Controls (n=20)	SLE vs RA	SLE vs Controls	RA vs Controls
RBCs ($\times 10^{12}/L$)	3.35±0.19	4.42±0.15	4.9±0.27	<0.001	<0.001	NS
WBCs ($\times 10^9/L$)	5.69±0.81	7.7±0.6	6.00±0.47	<0.05	NS	NS
Platelets ($\times 10^9/L$)	273±25.4	346.4±24.8	225±21.4	<0.05	NS	<0.05
Hb (g/dL)	9.2±0.59	12.4±0.42	13.9±0.56	<0.001	<0.001	NS
ESR ₁ (mm/h)	104±6.63	65.3±6.2	7.7±0.39	<0.001	<0.001	<0.001
ESR ₂ (mm/h)	121.4±5.26	91.3±5.5	16.6±0.42	<0.001	<0.001	<0.001
CRP (mg/L)	13 (65%)	14 (70%)	0 (0%)	NS	<0.001	<0.001
RF	6 (30%)	16 (80%)	0 (0%)	<0.05	NS	<0.001
ANA	15 (75%)	5 (25%)	0 (0%)	<0.05	<0.001	NS
LE cells	18 (90%)	0 (0%)	0 (0%)	<0.001	<0.001	--
Albuminuria	9 (45%)	0 (0%)	0 (0%)	<0.05	<0.05	--

NS= not significant.

Table 3 shows the values of T₃, T₄, TSH, ATGAb and TPOAb in SLE, RA and control groups. The mean value of T₄ was significantly higher in RA versus controls ($P<0.05$) but within normal range. The percentages of ATGAb were 5% in SLE and 30% in RA groups versus 10% in controls.

The percentage of TPOAb was 15% in SLE and 5% in RA versus 10% in controls. Only one patient with RA had both antibodies. The titres of both antibodies were insignificantly higher in SLE and RA patients versus controls (Fig. 1 & 2).

Table 4 shows the patterns of thyroid dysfunction in SLE and RA groups. Significantly higher percentages of abnormal thyroid function were found in SLE as compared with RA groups ($P < 0.05$) (Fig. 3). The percentages of patients with subclinical hypothyroidism (normal T_3 , T_4 and raised TSH) were 10% in SLE and RA groups. Percentages of patients with biochemical hypothyroidism (normal or decreased T_3 , decreased T_4 and increased TSH) were 10% in

SLE group and 0% in RA group. The percentages of patients with euthyroid sick syndrome (decreased T_3 , normal or decreased T_4 and normal TSH) were 20% in SLE group and 0% in RA group. Percentages of patients with subclinical hyperthyroidism (normal T_3 , T_4 and decreased TSH) were 5% in SLE and RA group. The percentages of patients with biochemical hyperthyroidism (increased T_3 , T_4 and decreased TSH) were 5% in SLE group and 0% in RA group (Fig. 4).

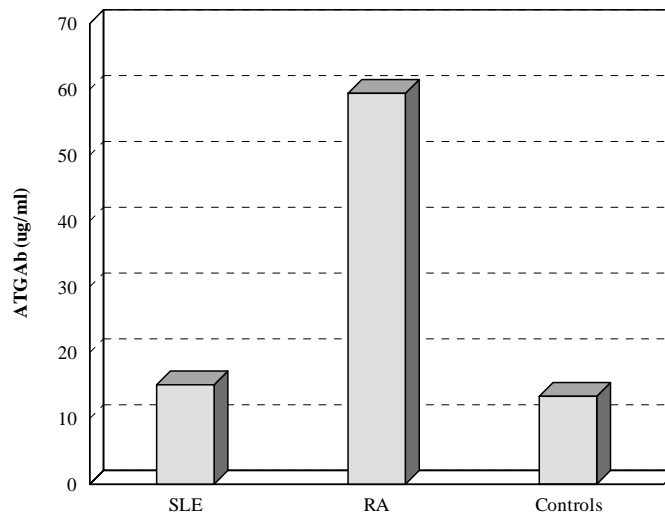


Figure 1. ATGAb levels in SLE, RA and control groups.

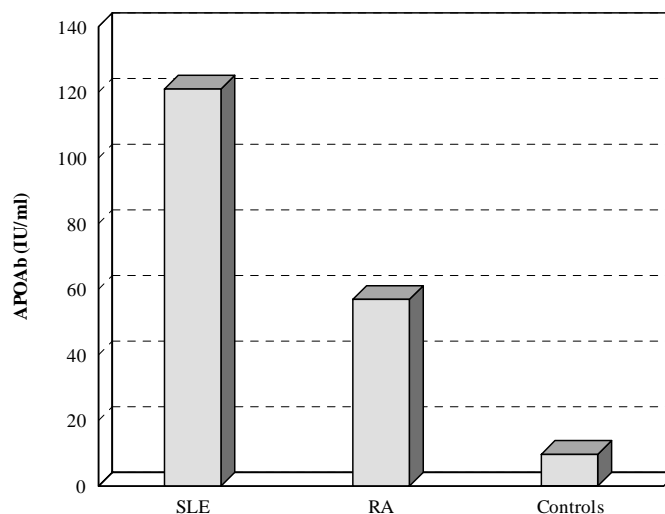


Figure 2. APOAb levels in SLE, RA and control groups.

Table 3. Thyroid hormones and thyroid antibodies in SLE , RA and control groups

Parameters	Groups			P value		
	SLE (n=20)	RA (n=20)	Control (n=20)	SLE vs RA	SLE vs Control	RA vs Control
T ₃ :						
Normal (82-179 ng/dL)						
- Mean±SE	136.6±14.13	142.1±7.6	145.2±8.93	NS	NS	NS
T ₄ :						
Normal (4.5-12.5 µg/dL)						
- Mean±SE	8.83±1.2	10.5±0.47	8.37±0.64	NS	NS	<0.05
TSH:						
Normal (0.4-4 µIU/mL)						
- Mean±SE	4.15±1.27	2.32±0.56	1.34±0.28	NS	NS	NS
ATGAb:						
Normal (2-50 ng/mL)						
- Mean±SE	15.12±11.5	59.4±24.5	13.38±7.72	NS	NS	NS
- No. (%) above normal	1 (5%)	6 (30%)	2 (10%)			
TPOAb:						
Normal (<35 IU/mL)						
- Mean±SE	121±65.4	56.9±48.4	9.7±4.78	NS	NS	NS
- No. (%) above normal	3 (15%)	1 (5%)	2 (10%)			
- Both antibodies	--	1 (5%)	--			

NS = not significant

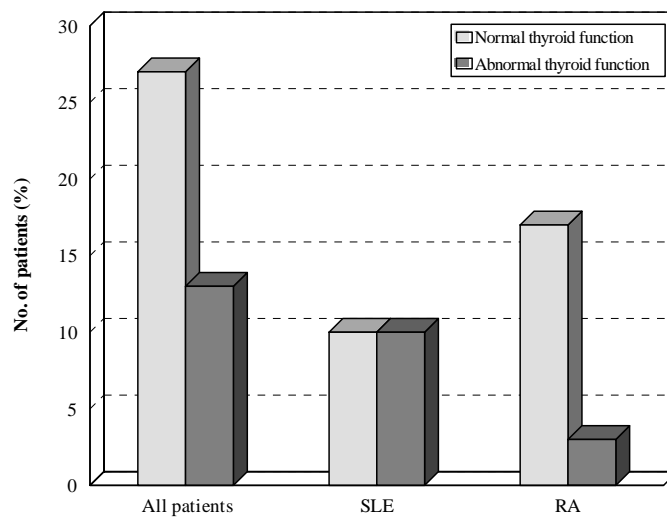


Figure 3. Percentage of thyroid dysfunction in all patients, SLE, and RA groups.

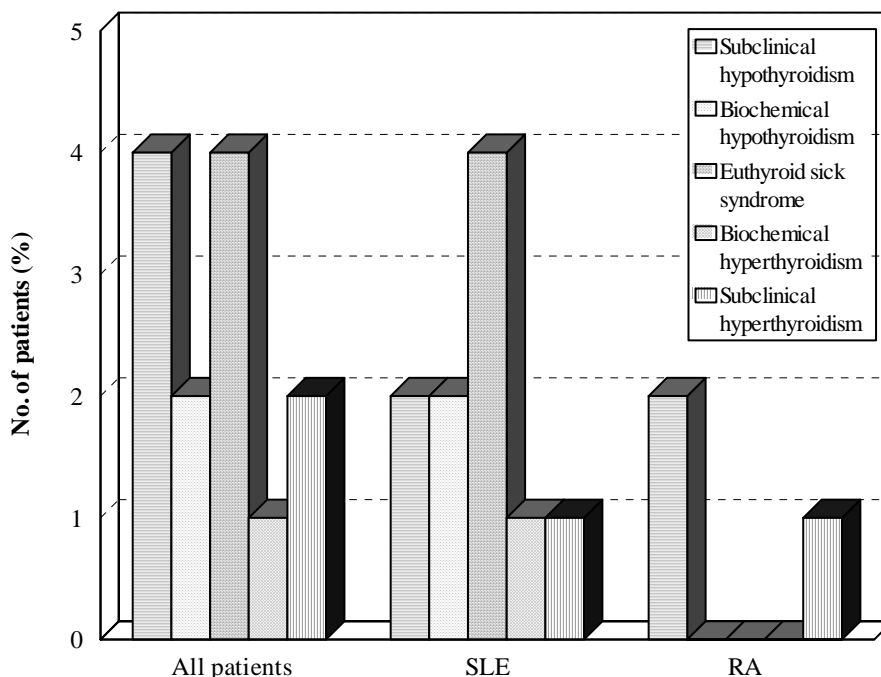


Figure 4. Patterns of thyroid dysfunction in all patients, SLE, and RA groups.

Table 4. Patterns of thyroid dysfunction in RA and SLE groups.

	All patients (n=40)	SLE (N=20)	RA (n=20)	P value
Normal thyroid function	27 (67.5%)	10 (50%)	17 (85%)	<0.05
Abnormal thyroid function	13 (32.5%)	10 (50%)	3 (15%)	<0.05
Subclinical hypothyroidism	4 (10%)	2 (10%)	2 (10%)	
Biochemical hypothyroidism	2 (5%)	2 (10%)	0	
Euthyroid sick syndrome	4 (10%)	4 (20%)	0	
Biochemical hyperthyroidism	1 (2.5%)	1 (5%)	0	
Subclinical hyperthyroidism	2 (5%)	1 (5%)	1 (5%)	

Table 5. shows the result of ANA, ATGAb and TPOAb in different patterns of thyroid disorders. 50% of patients with subclinical hypothyroidism had ATGAb (all with RA). All patients with biochemical hypothyroidism had TPOAb (all with SLE). 50% of patients with subclinical hyperthyroidism had ATGAb (with RA). One RA patient had both

antibodies and T₃ and T₄ were normal while TSH was at the lower limit of normal values (0.4 μ IU/mL).

We found no correlations between some activity parameters (morning stiffness, Ritchie index, number of active joints, ESR1 and ESR2) with titres of ATGAb and TPOAb.

Table 5. ANA, ATGAb and APOAb in different patterns of thyroid disorder.

Variables (No.)	ANA [No. (%)]	ATGAb [No. (%)]	APOAb [No. (%)]
Normal thyroid (27)	11 (40.7%)	4 (14.8%) 3 RA 1 SLE	2 (7.4%) 1 SLE 1 RA
Subclinical hypothyroidism (4)	1 (25%)	2 (50%) (2 RA)	--
Biochemical hypothyroidism (2)	2 (100%)	--	2 (100%) (2 SLE)
Euthyroid sick syndrome (4)	4 (100%)	--	--
Subclinical hyperthyroidism (2)	1 (50%)	1 (50%) (RA)	--
Biochemical hyperthyroidism (1)	1 (100%)	--	--

Discussion

We determined the degree of overlap between autoimmune thyroid diseases and two non-organ specific autoimmune diseases; SLE and RA. Although the prevalence of thyroid disorders is probably greater in SLE than in general population, controversial results were reported (Pyne and Isenberg, 2002). There are also differences in the prevalence of thyroid disorders in RA patients as shown in various studies (Chan et al., 2001; Del Puente et al., 2003).

The results of this study showed that thyroid dysfunction in SLE was 50% versus 15% in RA ($P < 0.05$). Chan et al (2001) reported thyroid dysfunction in 24.6% in SLE and 10.9% in RA patients. Stram et al (1994) reported abnormal thyroid function in 21.4% in SLE and 12.5% in RA patients. In a Korean population, Park et al (1995) found abnormal thyroid function in 28.6% of SLE patients. Tsai et al., (1993) found that 22.2% of their SLE Chinese patients had thyroid dysfunction. Moreover, Shiroky et al (1993) found abnormal thyroid function in 30% of RA patients.

Euthyroid sick syndrome is a functional thyroid disorder in nonthyroidal illness. It is usually normalized with treatment of the underlying diseases. The prevalence of euthyroid sick syndrome, which was the most

thyroid dysfunction in SLE patients in this study, was 20%. Two SLE patients (10%) had subclinical hypothyroidism, 2 patients (10%) had biochemical hypothyroidism, 1 SLE patient (5%) had biochemical hyperthyroidism and 1 SLE patient (5%) had subclinical hyperthyroidism. These results were in agreement with the report of Park et al., (1995) who found euthyroid sick syndrome in 14.3% followed by biochemical hypothyroidism in 7.9% of SLE patients. However, Chan et al (2001) found that subclinical hypothyroidism is the most common thyroid disorder (13%) of SLE patients, followed by clinical hypothyroidism (4.3%), biochemical and subclinical hyperthyroidism (2.9% for both) and only 1.5% for euthyroid sick syndrome.

Our study showed that subclinical and biochemical hypothyroidism (20%) were more common than biochemical and subclinical hyperthyroidism (10%). These results are consistent with those of Tsai et al (1993) who found that Hashimoto's thyroiditis (8.8%) was more common than thyrotoxicosis (2.2%). Pyne and Isenberg (2002) reported that the prevalence of 5.7% hypothyroidism in SLE cohort was higher than in normal population (1%), while that of hyperthyroidism (1.7%) was not significantly different. On contrast, some previous studies

found that SLE patients had more thyrotoxicosis than Hashimoto's thyroiditis. Goh and Wang (1986) reported that thyrotoxicosis (2.8%) was more common than hypothyroidism (0.9%) in their studied SLE Asians population. They also found that nontoxic goitre was not an uncommon abnormality in patients with SLE.

In the present study, 2 RA patients had subclinical hypothyroidism (10%) and 1 RA patient had subclinical hyperthyroidism (5%). These results are consistent with the results of Chan et al (2001) who reported hypothyroidism in 9.4% of RA patients (clinical and subclinical) and subclinical hyperthyroidism in only 1.6%. Also, Al-Awadhi et al (1999) reported a higher prevalence of hypothyroidism among Arabs with RA, with higher prevalence of subclinical hypothyroidism (14.58%). Del Puente et al (2003) found subclinical hypothyroidism in (21%) of newly diagnosed RA patients. In contrast, Youinou et al (1987) showed no difference between patients with RA and controls. Chan et al (2001) reported that SLE in particular and RA may confer an autoimmune locus for earlier development of hypothyroidism and these patients represent a pool from which cases of organ-specific autoimmune diseases emerge. The differences in these results could be explained by racial differences, patients selection (age, sex), size of sample, duration of follow-up, influence of medications and diagnostic methods for the detection of thyroid disorders.

In SLE patients TPOAb and ATGAb were detected in 15% and 5%, respectively as compared with 10% for both antibodies in controls. Moreover, the titres of ATGAb and TPOAb were higher (but insignificant) in SLE patients than in controls. Pyne and Isenberg (2002) showed that the prevalence of TPOAb was 3.7% and of ATGAb was 1% in SLE patients. Park et al (1995) reported TPOAb and ATGAb to be 20.6% and 27% respectively in SLE. Also, Chan et al (2001)

reported positive TPOAb in 23.2% in their study group. It has been shown that the percentages of individuals with antithyroid antibodies increased with age (being ~ 10% in women under 18 years of age) and increases two to four fold after the age of 60 years with rates of 30 % among females > 70 years of age (Mariotti et al., 1992).

In RA patients, ATGAb was detected in 30% while TPOAb was detected in 5% and both antibodies were detected in 5%. Chan et al (2001) reported that the prevalence of TPOAb was 10.9% in RA patients. Del Puente et al (2003) reported ATGAb in 25% and TPOAb in 32% in newly diagnosed RA patients. They explained the high percentages of antithyroid antibodies on the basis of lack of any medications being given to their study subjects.

In the present study, all SLE patients with biochemical hypothyroidism had positive TPOAb. This result was in agreement with the studies of Chan et al (2001) and Pyne and Isenberg (2002). Also 50% of patients with subclinical hypothyroidism had ATGAb; all of them had RA. We failed to detect TPOAb or ATGAb in SLE with subclinical hypothyroidism. This may be explained by their younger age and short duration of disease, needing longer time to develop antithyroid antibodies.

Previous studies have shown that a number of patients with subclinical hypothyroidism will go on to develop clinical hypothyroidism (Norbyke et al., 1993). The risk factors for this progression are greater age, female gender and positive antithyroid antibodies (Vanderpump et al., 1995). We also found positive ATGAb in RA patients with subclinical hyperthyroidism. Also, the only patients with both antibodies had lower limit of TSH (0.4 μ IU/mL) but normal T₃ and T₄ and this patient may develop subclinical hyperthyroidism. Chan et al (2001) found TPOAb in all RA patients with hyperthyroidism.

The mechanism for coexistence of both autoimmune thyroid disease and the two autoimmune diseases are unknown; however, several mechanisms may contribute. Autoreactive T cells which can cause primary thyroid destruction as well as polyclonal B cell activation in the two autoimmune rheumatic diseases may induce autoimmune thyroiditis and SLE or RA in the same patients. It is also possible that autoimmune thyroid disease is secondary to the production of thyrotropin by activated lymphocytes or autoantibodies against the thyroid, its hormone, or receptors. Other factors, such as genetic and environmental factors may be involved (Park et al., 1995; Chan et al., 2001).

In summary, we found that 50% of SLE and 15% of RA patients frequently showed abnormal results of thyroid function test. These abnormalities are more implicated with euthyroid sick syndrome and hypothyroidism (subclinical and overt) than hyperthyroidism in SLE patients. SLE and RA were associated with antithyroid antibodies (TPOAb in SLE and ATGAb in RA).

We recommend, assessment of thyroid function and measurement of thyroid antibodies as a part of biochemical and immunological profile of SLE and RA patients.

References

1. Al-Awadhi AM, Olus SO, Al-Zoid NS, Prabha K, Al-Ali N and Al-Jarallah KH (1999): Prevalence of hypothyroidism among Arabs with rheumatoid arthritis. *Rheumatology*; 38: 472-482.
2. Arnett FC, Edworthy SM, Bloch DA et al (1988): The American Rheumatism Association 1987 revised criteria for classification of RA. *Arthritis Rheum*; 31: 315-324.
3. Boey ML, Fong PH, Lee JSC, Ng WY and Thai AC (1993): Autoimmune thyroid disease in SLE in Singapore. *Lupus*; 2: 51-54.
4. Caron PH, Lassoued S, Domer O, Oksman F and Founie A (1992): Prevalence of thyroid abnormalities in patients with rheumatoid arthritis. *Thyroidol Clin Exp*; 4: 99-102.
5. Chan ATY, Soffar AL and Bucknall RC (2001): Thyroid disease in systemic lupus erythematosus and rheumatoid arthritis. *Rheumatology*; 40: 353-354.
6. Del Puente A, Esposito A, Savastano S, Lupoli G and Nuzzo V (2003): High prevalence of thyroid autoantibodies in newly diagnosed rheumatoid arthritis patients. *Clin Exp Rheumatol*; 1: 137.
7. Goh KL and Wang F (1986): Thyroid disorders in systemic lupus erythematosus. *Ann Rheum Dis*; 45: 579-583.
8. Gordon MB, Klein I, Dekker S, Rodnan GP and Medsger TA (1981): Thyroid disease in progressive systemic sclerosis: increased frequency of glandular fibrosis and hypothyroidism. *Ann Intern Med*; 95: 431-435.
9. Inukai T and Takemura Y (1999): Antithyroid peroxidase antibody. *Nippon Rinsho*; 57: 18519-18523.
10. Mariotti S, Sansoni P, Barbesino G et al (1992): Thyroid and other organ specific autoantibodies in healthy centenarians. *Lancet*; 339: 1506-1508.
11. MasukoHongo K and Kato T (1999): The association between autoimmune thyroid diseases and rheumatic diseases. *Nippon Rinsho*; 57: 1873-1877.
12. Miller FW, Moore GF, Weintraub BD, Steinberg AD and Burman KD (1993): Thyroid stimulating and thyrotropin binding-inhibitory immunoglobulin activity in patients with systemic lupus erythematosus having thyroid function abnormalities. *Thyroid*; 1: 229-234.
13. Nordyke RA, Gilbert FI Jr, Miyamoto LA and Flensy KA (1993): The superiority of antimicrosomal over antithyroglobulin antibodies for detecting Hashimoto's thyroiditis. *Arch Intern Med*, 153: 862-865.
14. Park DJ, Cho CS, Lee SH, Park SH and Kim HY (1995): Thyroid disorders in Korean patients with systemic lupus erythematosus. *Scand J Rheumatol*; 24: 13-17.
15. Perez EB, Krans A, Lopez G, Ciguentes M and Alarcon-Segovia D (1995): Autoimmune thyroid disease in primary Sjogren's syndrome. *Am J Med*; 99: 480-484.

16. Pyne D and Isenberg DA (2002): Autoimmune thyroid disease in systemic lupus erythematosus. *Ann Rheum Dis*; 61: 70-72.
17. Ritchie DM, Boyle JA, McLnness JM, Jasani MK, Dalakos TG, Grieverson P and Buchanan WW (1968): Clinical studies with an articular index for the assessment of joint tenderness in patients with rheumatoid arthritis. *Q J Med*; 37: 393.
18. Shiroky JB, Cohen M, Ballachey ML and Neville C (1993): Thyroid dysfunction in rheumatoid arthritis: A controlled prospective survey. *Ann Rheum Dis*; 53: 454-456.
19. Stram K, Fuster V, Pins V and Kozual K (1994): Changes in thyroid function in systemic lupus erythematosus progressive systemic sclerosis and rheumatoid arthritis. *Rheumatizm*; 41: 1-4.
20. Tan EM, Cohen AS, Fries JF et al (1982): The revised criteria for the classification of SLE. *Arthritis Rheum*; 25: 1271-1277.
21. Tsai RT, Chang TC, Wang CR, Chuang CY and Chen CR (1993): Thyroid disorders in Chinese patients with systemic lupus erythematosus. *Rheumatol Int*; 13: 9-13.
22. Vanderpump MP, Tunbridge WM, French JM et al (1995): The incidence of thyroid disorders in the community. A twenty year follow up of the Wickham survey. *Clin Endocrinol*; 43: 55-68.
23. Weiss EX and Shoenfeld Y (1991): Shifts in autoimmune diseases: The kaleidoscope of autoimmunity. *J Med Sci*; 27: 215-217.
24. Williams, RH (1998): Laboratory test of thyroid hormone economy. In: Williams (ed), *Textbook of Endocrinology*, P.W.B. Saunders, Philadelphia.
25. Wiseman P, Stewart K and Rai GS (1989): Hypothyroidism in polymyalgia rheumatica and giant cell arteritis. *BMJ*; 298: 647-648.
26. Youinou P, Mangold DW, Jonquon J, Swirsky H, Legoff P and Sherbaun WA (1987): Organ specific autoantibodies in non organ specific autoimmune diseases with special reference to rheumatoid arthritis. *Rheumatol Int*; 7: 123-6.