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Thyroid Dysfunction in Patients with Systemic Connective Tissue Disease

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Abstract

Background. Alterations in the circulating thyroid hormone concentrations constituting the euthyroid sick syndrome (ESS) are frequently associated with systemic non-thyroidal diseases such as systemic connective tissue disease (SCTD).

Aim. to elucidate the pattern of thyroid dysfunction in patients with SCTD.

Subjects and Methods. Thirty patients with systemic lupus erythematosus (SLE) and thirty rheumatoid arthritis (RA) patients in addition to 30 healthy age- and sex- matched controls were recruited from the Internal Medicine Department of Ain- Shams University Hospital. Thyroid stimulating hormone (TSH), thyroid hormones including T3 and T4, antithyroglobulin antibodies (ATGAb), thyroid peroxidase antibodies (TPOAb), ESR, RF, ANA, LE cells and CRP were determined.

Results. 46.6 percent of SLE patients showed thyroid dysfunction compared to 16.6% of RA ($P<0.05$). In SLE group, 20% had euthyroid sick syndrome, 16 % had hypothyroidism (10% subclinical and 6% overt), and 9% had hyperthyroidism (3% subclinical and 6% overt). However in RA, 13% had hypothyroidism (10% subclinical and 3% overt) and 3% had subclinical hyperthyroidism. TPOAb was found in 16% of SLE and 6% in RA patients. Also ATGAb was found in 6% of SLE and 30% in RA patients and 10% of controls, but the titers were higher in the patients.

Conclusion. Thyroid dysfunction was common in patients with SCTD and they were associated with antithyroid antibodies.

Introduction

Autoimmune diseases are clearly associated with many factors, such as genetic, hormonal and environmental as well as immune defects (1). These factors, referred to as the mosaic of autoimmunity, can interact in diversity of autoimmune diseases and the association of these diseases in the same patients (2). 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 (3). These associations include SLE (3-5), RA (6, 7), Sjogren syndrome (8), scleroderma and vasculutides (9, 10). Patients with non-thyroidal illness (NTI) frequently have changes in serum thyroid hormone measurements that may suggest thyroid dysfunction, they have very low circulating concentrations of total and absolute free triiodothyronine (T3), low-normal concentrations of total thyroxin (T4), elevated concentrations of absolute free T4, and circulating concentrations of thyroid stimulating hormone (TSH) that are either normal or subnormal (11). Hesch, 1981 has

reported that these low levels are commonly compensated for by simultaneous elevation in the thyroid stimulating hormone level. Consequently, the patients are usually clinically euthyroid (12). This is referred to as the euthyroid sick syndrome (ESS) (13).

A number of studies have suggested that thyroid disease is more common in SLE than in the general population, but there is disagreement as to whether both hypothyroidism and hyperthyroidism are more common (3, 5), or whether this finding is restricted to hypothyroidism alone (14).

Both ATGAb and TPOAb have been found with greater frequency in SLE than in the general population, even in SLE patients who do not have clinical thyroid disease (14).

The incidence of autoimmune thyroiditis in patients with RA is variable. Hypothyroidism (subclinical and overt) was the most frequent thyroid disease associated with RA (6, 14, 15). RA occurs with high incidence in association with positive antithyroid antibodies (15, 16).

The current study was planned to study the possible relation between thyroid hormone level changes in patients with SCTD.

Materials and Methods

This study included thirty patients with systemic lupus erythematosus (SLE), (25 female (83%) & 5 males (17%); aged 35.1 ± 1.6) and thirty patients with rheumatoid arthritis (RA), (20 females (66.6%) & 10 males (17.4%); aged 26.8 ± 1.7) in addition to 30 healthy age- and sex- matched controls (50% female &50% male; aged 42.1 ± 1.5), were recruited from the Internal Medicine Department of Ain-Shams University Hospital.

RA and SLE were diagnosed according to the classification criteria for RA arthritis and SLE of the American Rheumatism Association (17, 18). Patients from both groups were found not to be in a flare of their disease based on the SLE disease activity index (SLEDAI) for the SLE group and joint scores/ acute-phase response for the RA group.

RA was diagnosed if at least four of the seven following criteria were present: morning stiffness, arthritis of three or more joint areas/hand joints, symmetric arthritis, rheumatoid nodules, serum rheumatoid factor and typical radiographic changes. SLE was defined if at least four of the following 11 criteria were present: malar rash, discoid rash, photosensitivity, oral ulcers, arthritis, serositis, renal disorder, neurological disorder, haematological disorder, antinuclear antibody and/or other immunological disorder.

The duration of the disease was 22.9 ± 0.3 months for SLE patients and 33 ± 2.3 months for RA patients. Exclusion criteria were any patient with known or clinically suspected thyroid dysfunction. All patients in this study were free of immunosuppressant or corticosteroid medications. RA patients were on low dose of methotrexate (10 mg/week) and SLE patients on hydroxychloroquine (250 mg/day).

All patients and controls gave informed consent and the study was approved by the Institutional Ethical Committee of the National Research Center (Cairo-Egypt) according to the 1983 revised Helsinki declaration of 1975.

All patients and controls were subjected to complete history taking, thorough clinical examination and to the following investigation:

1. Erythrocyte sedimentation rate (ESR) using Westergreen method.

2. C-reactive protein (CRP) measured by Humatex latex agglutination slide for the qualitative and semi quantitative determination of CRP.

3. Rheumatoid factor (RF) measured by using Stanbio RA factor latex agglutination slide for the qualitative and semi quantitative determination of RF in serum.

4. Antinuclear antibodies (ANA) done by ANAFIDR test which is an indirect florescent antibody test. The kit was supplied by Diasorin, Minnesota, USA.

5. Lupus erythematosus cell (LE cell) measured by using Stanbio RAPET SLE latex agglutination slide test for the quantitative determination of anti-deoxyribonucleic protein (DNP) associated with SLE in human serum.

6. The ultra sensitive human thyroid stimulating hormone (hTSH II) was measured using a Microparticle Enzyme Immunoassay (MEIA) for the quantitative determination of TSH in the human serum on the AxSYM system (Abbott Laboratories, Abbot Park, USA) (19).

7. The free serum T3 level was determined using the MEIA method for quantitative estimation of free triiodothyronin in human serum on AxSYM

system (Abbott Laboratories, Abbot Park, USA) (20).

8. The total serum T4 level was measured using the Fluorescence Polarization Immunoassay (FPIA) method for the quantitative determination of thyroxin (T4) in human serum on AxSYM system (Abbott Laboratories, Abbot Park, USA) (21).

9. Antithyroglobulin antibodies (ATGAb) using an indirect solid phase enzymeimmunometric assay (ELISA) kit from Organteck (20).

10. Thyroid peroxidase antibodies (TPOAb) using Immulite analyzer kit supplied by Diagnostic Product Corporation, CA, USA (20).

Statistical Analysis

Variables are given as mean and standard deviation (SD) unless stated otherwise. The significance of difference between 2 sets of variables was assessed by the student t-test and chi square. Correlation coefficient test (r-test) was used to detect the significance for correlation between two quantitative variables (Pearson correlation).All analysis was performed using the Statistical Package for Social Science (SPSS) version 10.0.

Results

Tables 1 & 2 represent clinical data of SLE and RA patients. The duration of illness was 22.9 ± 0.3 months for SLE patients and 33 ± 2.3 months for RA patients. Arthritis was found in 50% of SLE patients and kidney affection in 43%. Duration of morning stiffness was 60.2 ± 21 minutes in RA and Ritchie index was 15 ± 5.

Table 1: Clinical data of SLE patients presented as mean ± SD or percentages.

Variables	SLE patients (n=30)
Age(years)	35.1±1.6
Gender (females/males)	25/5 (83%/17%)
Duration (months)	22.9 ± 0.3
Malar flush	28 (93%)
Photosensitivity	26 (86%)
Arthritis	15 (50%)
Discoid lupus	11 (36%)
Oral ulcerations	10 (33%)
Serositis	10 (33%)
Renal affection	13 (43%)
Fever	20 (66.6%)

Table 3 shows peripheral hemogram, ESR, CRP, RA and ANA in patients and controls group.

Table 2: Clinical data of RA patients presented as mean ± SD or percentages.

Variables	RA patients (n=30)
Age(years)	26.8 ± 1.7
Gender (females/males)	20/10 (66.6%/33.3%)
Duration (months)	33 ± 2.3
Morning stiffness (minutes)	60.2 ± 21
Ritchie index	15 ± 5
Deformity	6 (20%)

The mean values of Hb and RBCs were significantly lower in SLE vs. controls (P<0.001 for both). The mean values of platelets were significantly higher in RA vs. SLE (P<0.05). The mean ESR and the percentage of CRP were significantly higher in SLE and RA vs. 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 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 3: Laboratory parameters in patients and control groups presented as mean ± SD or percentages.

Parameters	SLE N=30	RA N=30	Controls N=30	SLE vs. RA	SLE vs. controls	RA vs. controls
RBCs ($X10^{12}$/l)	3.4 ± 0.2	4.4 ± 0.2	4.9 ± 0.3	<0.001	<0.001	NS
WBCs($X10^{9}$/l)	5.7 ± 0.8	7.7 ± 0.6	6.0 ± 0.5	<0.05	NS	NS
platelets ($X10^{9}$/l)	273 ± 25	346 ± 25	225 ± 21	<0.05	NS	<0.05
Hb (g/dl)	9.2 ± 0.6	12.4 ± 0.4	13.9 ± 0.6	<0.001	<0.001	NS
ESR (mm/hr)	121 ± 5	91 ± 5.5	16 ± 0.5	<0.001	<0.001	<0.001
CRP mg/L)	15 (50 %)	20 (66.6%)	0 (0%)	NS	<0.001	<0.001
RF	6 (20%)	25 (83%)	0 (0%)	<0.05	NS	<0.001
ANA	22 (73%)	5 (17%)	0 (0%)	<0.05	<0.001	NS
LE cells	28 (93%)	0 (0%)	0 (0%)	<0.001	<0.001	--
Albuminuria	13 (43%)	0 (0%)	0 (0%)	<0.05	<0.05	--

Table 4 shows serum T3, T4, TSH, ATGAb and TPOAb in patients and control groups. The mean value of T4 was significantly higher in RA vs. controls (P<0.05) but within normal range. The percentages of positive ATGAb were 6% in SLE and 30% in RA versus 10% in controls. The percentages of positive

Table 4: Thyroid hormones and thyroid antibodies in patients and control group.

Groups parameters	SLE N=30	RA N=30	Control N=30	SLE vs. RA	SLE vs. control	RA vs. control
Serum T3 Above n(%)] Below [n(%)]	136 ±14 3 (10%) 7 (25%)	142 ± 7.6 0 (0%) 0 (0%)	145 ± 8.9	NS	NS	NS
Serum T4 Above n(%)] Below [n(%)	8.8 ± 1.2 3 (10%) 6 (20%)	10.5 ± 0.5 0 (0%) 0 (0%)	8.4 ± 0.6	<0.05	<0.05	NS
Serum TSH Above n(%)] Below [n(%)	4.2 ± 1.3 6 (20%) 5 (16%)	2.3 ± 0.6 3 (10%) 2 (6%)	1.3 ± 0.3	NS	NS	NS
ATGAb [n(%)] above normal	15 ±11.5 2 (6%)	59 ± 24.5 9 (30%)	13.4 ± 7.7 3 (10%)	NS	NS	NS
TPOAb [n(%)] above normal	121± 65 5 (16%)	57 ± 48 2 (6%)	9.7 ± 4.8 3 (10%)	NS	NS	NS
Both antibodies	--	2 (6%)	--	NS	NS	NS

Normal values: T3: 82-179 ng/ml, T4:4.5-12.5 ìg/ml, TSH: 0.4-12.5 ìIU/ml, ATGAb: 2-50 ng/ml, TPOAb: < 35 IU/ml. NS = not significant; TPOAb = Thyroidperoxidase antibody; ATGAb = Antithyroglobulin antibody; SLE= systemic lupus erythematosus; RA= rheumatoid arthritis.

TPOAb were 16% in SLE, 6% in RA versus 10% in controls. Only two patients with RA had both antibodies. The mean titers of both antibodies were insignificantly higher in SLE and RA patients versus controls.

Table 5 shows the patterns of thyroid dysfunction in patients with systemic connective tissue disease. Significantly higher percentages of abnormal thyroid function were found in SLE than RA groups (P<0.05). The percentages of patients with subclinical hypothyroidism were 10% in SLE and RA groups. The percentages of patients with overt hypothyroidism were 6.6% in SLE and 3.3% in RA group. The percentages of patients with euthyroid sick syndrome were 20% in SLE and 0% in RA group. The percentages of patients with subclinical hyperthyroidism were 3.3% in SLE and RA group. The percentages of patients with overt hyperthyroidism were 6.6% in SLE group and 0% in RA group.

Table 5: Thyroid dysfunction in RA and SLE groups.

	All patients N=60	SLE N=30	RA N=30	P value
Normal thyroid function	41 (68.3%)	16 (53%)	25 (83.3%)	<0.05
Abnormal thyroid function	19 (31.6%)	14 (46.6%)	5 (16.6%)	<0.05
Subclinical hypothyroidism	6 (10%)	3 (10%)	3 (10%)	NS
Overt hypothyroidism	3 (5%)	2 (6.6%)	1 (3.3%)	NS
ESS	6 (10%)	6 (20%)	0	NS
Overt hyperthyroidism	2 (3%)	2 (6.6%)	0	NS
Subclinical hyperthyroidism	2 (3.3%)	1 (3.3%)	1 (3.3%)	NS

ESS: euthyroid sick syndrome.

Table 6 shows ANA, ATGAb and TPOAb in the different patterns of thyroid dysfunction in our patients. Fifty percent of patients with subclinical hypothyroidism had ATGAb (1 SLE and 2 RA). All patients with overt hypothyroidism had TPOAb (all with SLE). 50% of patients with subclinical hyperthyroidism had ATGAb (1 RA).

Table 6: ANA, ATGAb and TPOAb in the different patterns of thyroid dysfunction in patients.

Variables	ANA [no (%)]	ATGAb [no (%)]	TPOAb [no (%)]
Normal thyroid function (41)	13 (31.7%)	6 (14.6%) RA	4 (9.7%) 2 SLE , 2 RA
Subclinical hypothyroidism (6)	2 (33%)	3 (50%) 1 SLE, 2 RA	--
Overt hypothyroidism (3)	3 (100%)	--	3 (100%) 3 SLE
ESS (6)	6 (100%)	--	--
Subclinical hyperthyroidism (2)	1 (50 %)	1 (50%) 1 RA	--
Overt hyperthyroidism (2)	2 (100%)	--	--

Two RA patients had both antibodies and T3 and T4 were normal while TSH were at the lower limit of normal (0.4 ìIU/ml).

Discussion

We have determined the degree of overlap between autoimmune thyroid diseases and patients with systemic connective tissue diseases, SLE and RA. The mechanisms for coexistence of both autoimmune thyroid diseases and the two non-organ specific autoimmune disease, SLE and RA are unknown; however several mechanisms may contribute. Auto reactive 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 patient. It is also possible that autoimmune thyroid disease is secondary to the production of thyrotropin by activated lymphocytes or auto antibodies against the thyroid, its hormone, or receptors. Other factors such as genetic and environmental factors may be involved (1, 15).

Although the prevalence of thyroid disorders is probably greater in SLE than in the general population, controversial results were reported (3). There are also differences in prevalence of thyroid disorders in RA patients in various studies (7, 14).

Kochi et al., 2005 (22), found an associations between the SNP and susceptibility to autoimmune thyroid disease and systemic lupus erythematosus. FCRL3 may therefore have a pivotal role in autoimmunity; on the other hand a genetic linkage effect in a region of D5S1462 on the chromosome 5q14.3-15 was already demonstrated between two related autoimmune condition – SLE and thyroid disease (23), These results suggest that stratifying SLE pedigrees by the presence of other autoimmune disorders may facilitate the discovery of genes related to SLE and that 5q14.3-15 harbors a susceptibility gene shared by SLE and AITD (23).

Our study showed thyroid dysfunction in 46.6% of SLE vs. 16.6% in RA patients (P<0.05). This is consistent with the previous result of El-Sherif et al., 2004 (24), who reported thyroid dysfunction in 50% in SLE vs. 15% in RA patients as well as Chan et al., 2001 (7) who reported thyroid dysfunction in 24.6% in SLE and 10.9% in RA patients. Stram et al., 1994 (25) have reported abnormal thyroid function in 21.4% in SLE and 12.5% in RA patients. Tsai et al., 1993 (5) found that 22.2% of their SLE patients had thyroid dysfunction.

Thyroid dysfunction is not uncommon in SLE and RA; however the pattern of abnormality is variable. In this study, we found that 6 SLE patients had euthyroid sick syndrome (20%), 3 SLE patients (10%)

had sub clinical hypothyroidism. 2 SLE patients (6.6%) had overt hypothyroidism. 2 SLE patients (6.6%) had overt hyperthyroidism and 1 SLE patients (3.3%) had sub clinical hyperthyroidism. These results were in agreement with the report of Park et al., 1995 (1), who found ESS in 14.3% followed by biochemical hypothyroidism in 7.9% of SLE patients. However, Chan et al., 2001 (7), found sub clinical hypothyroidism in 13% of SLE patients, followed by clinical hypothyroidism (4.3%), overt and sub clinical hyperthyroidism (2.9% for both) and lastly ESS (1.5%).

Our results showed that ESS (20%) was more common than all other thyroid disorders.

Our results were consistent with those of Tsai et al., 1993 (5) who found that Hashimoto thyroiditis (8.8%) was more common than thyrotoxicosis (2.2%). Pyne and Isenberg, 2002 (3), found that the prevalence of 5.7% of hypothyroidism in SLE cohort was higher than in normal population (1%), while that of hyperthyroidism (1.7%) was not significantly different. In contrast, other studies found that SLE patients had more thyrotoxicosis than Hashimoto thyroiditis (26).

In the present study, 4 RA patients had hypothyroidism (3 sub clinical and 1 overt) (13.3%) and 1 had subclinical hyperthyroidism (3.3%). These results were consistent with others, who reported hypothyroidism in 9.4% of RA patients (7, 14); others reported high prevalence of hypothyroidism in RA patients (15). In contrast, others found no differences between patients with RA and controls (27). The differences in these results could be explained by racial differences, patient selection (age & sex), size of the sample, duration of follow up, influence of medications and diagnostic methods for the detection of thyroid disorders.

Thyroid autoantibodies are a secondary response to thyroid injury; together these antibodies increase the diagnostic sensitivity of autoimmune thyroid disease and possibly other diseases as well (28). TPOAb are antibodies against thyroid peroxidase enzyme, which catalyzes the iodination of tyrosine and the subsequent biosynthesis of T3 and T4 (29). ATGAb are antibodies against thyroglobulin, which is produced by the thyroid cells and stored in the thyroid colloid. High titers of TPOAb and ATGAb were found in Hashimoto thyroiditis and Graves's disease (29).

Our study found that ATGAb and TPOAb were detected in 6% and 16% respectively in SLE patients compared to 10% for both antibodies in controls. Moreover, the titers were higher but insignificant in patients than controls. Pyne and Isenberg, 2002 (3) showed that the prevalence of TPOAb was 3.7% and of ATGAb was 1% in SLE patients. Park et al., 1995 (1) reported TPOAb and ATGAb to be 20.6% and 27%, respectively in SLE patients' .In RA patients, we found that ATGAb was detected in 30% while TPOAb was detected in 6%, Chan et al., 2001 (7) reported that the prevalence of TPOAb was 10.9% in RA patients. It has been shown that the percentages of individuals with antithyroid antibodies increased with age (30).

In our study all SLE patients with overt hypothyroidism had positive TPOAb. This result was in agreement with others (3, 7). Also 50% of patients with subclinical hypothyroidism had ATGAb; 1 SLE & 2 RA.

Previous studies have shown that a number of patients with subclinical hypothyroidism will go on to develop clinical hypothyroidism (31). The risk factors for this progression was greater age, female gender and positive antithyroid antibodies (32). We also found positive ATGAb in RA patients with subclinical htperthyroidism. Also two patients with both antibodies had lower limit of TSH but normal T3 and T4 and those patients may develop subclinical hyperthyroidism. Chan et al., 2001 (7), found TPOAb in all RA patients with hyperthyroidism.

In conclusion, thyroid dysfunction was common in patients with SCTD and they were associated with antithyroid antibodies and we recommend assessment of thyroid function and measurement of thyroid antibodies as a part of biochemical and immunological profile of SLE and RA patients.

Disclosure of conflict of interest: all authors have no conflict of interest.

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